NOVEMBER 2001
VOLUME 46
NUMBER 11

# RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
46TH YEAR—ESTABLISHED 1956

## SPECIAL ISSUE

## EVIDENCE-BASED MEDICINE IN RESPIRATORY CARE PART I

- What Is EBM and Why Should It Be Practiced?
- Outcomes Research in Respiratory Care
- From Data to Evidence: Evaluative Methods in EBM
- Assessment of Health-Related QOL
- Translating Evidence into Practice: Pursuing Perfection in Pneumococcal Vaccination in a Rural Community
- The Evidence for Secretion Clearance Techniques
- Evidence-Based Management of COPD

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DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. In a 12-week clinical study, the most common adverse reactions reported with DuoNeb Inhalation Solution were chest pain, pharyngitis, diarrhea, bronchitis, nausea and leg cramps.

**Albuterol sulfate can have a significant cardiovascular effect, significant hypokalemia and the potential life-threatening paradoxical bronchospasm.** Caution is advised in patients with convulsive disorders, hyperthyroidism, diabetes mellitus, narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction. Co-administration of DuoNeb Inhalation Solution and other sympathomimetic agents may increase the risk of adverse cardiovascular effects.

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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator.

**CONTRAINDICATIONS**

DuoNeb is contraindicated in patients with a history of hypersensitivity to any of its components, or to atropine and its derivatives.

**WARNINGS**

**Paradoxical Bronchospasm:** In the clinical study of DuoNeb, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with both inhaled ipratropium bromide and albuterol products and can be life-threatening. If this occurs, DuoNeb should be discontinued immediately and alternative therapy instituted.

**Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive use of inhaled products containing sympathomimetic amines and with the home use of nebulizers.

**Cardiovascular Effect:** DuoNeb, like other beta adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon for DuoNeb at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, DuoNeb, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions to albuterol and/or ipratropium bromide may occur after the administration of DuoNeb as demonstrated by rare cases of urticaria, angioedema, rash, pruritus, oropharyngeal edema, bronchospasm, and anaphylaxis.

**PRECAUTIONS**

**General**

1. Effects Seen with Sympathomimetic Drugs: As with all products containing sympathomimetic amines, DuoNeb should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Additionally, β-agonists may cause a decrease in serum potassium in some patients, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation.

2. Effects Seen with Anticholinergic Drugs: Due to the presence of ipratropium bromide in DuoNeb, it should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction.

3. Use in Hepatic or Renal Diseases: DuoNeb has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in these patient populations.

**Information for Patients**

The action of DuoNeb should last up to 5 hours. DuoNeb should not be used more frequently than recommended. Patients should be instructed not to increase the dose or frequency of DuoNeb without consulting their healthcare provider. If symptoms worsen, patients should be instructed to seek medical consultation.

Patients must avoid exposing their eyes to this product as temporary papillary dilation, blurred vision, eye pain, or precipitation or worsening of narrow-angle glaucoma may occur, and therefore proper nebulizer technique should be assured, particularly if a mask is used.

If a patient becomes pregnant or begins nursing while on DuoNeb, they should contact their healthcare provider about use of DuoNeb.

See the illustrated Patient's Instruction for Use in the product package insert.

**Drug Interactions**

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is, therefore, advised in the co-administration of DuoNeb with other drugs having anticholinergic properties.

β-adrenergic agents: Caution is advised in the co-administration of DuoNeb and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

β-receptor blocking agents: These agents and albuterol sulfate inhibit the effect of each other. β-receptor blocking agents should be used with caution in patients with hyperreactive airways, and if used, relatively selective β, selective agents are recommended.

Diuretics: The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of β-agonist-containing drugs, such as DuoNeb, with non-potassium sparing diuretics.

Monoamine oxidase inhibitors or tricyclic antidepressants: DuoNeb should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents because the action of albuterol sulfate on the cardiovascular system may be potentiated.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Albuterol Sulfate: In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m² basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 20 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleous assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Ipratropium bromide: In 2-year studies in Sprague-Dawley rats and CD-1 mice, ipratropium bromide showed no evidence of tumorigenicity at oral doses up to 6 mg/kg (approximately 15 times and 8 times the maximum recommended daily inhalation dose for adults in rats and mice respectively, on a mg/m² basis).

Ipratropium bromide was not mutagenic in the Ames test and mouse dominant lethal test. Ipratropium bromide was not clastogenic in a mouse micronucleous assay.

A reproduction study in rats demonstrated decreased conception and increased resorptions when ipratropium bromide was administered orally at a dose of 90 mg/kg (approximately 240 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). These effects were not seen with a dose of 50 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

**Pregnancy**

*TERATOGENIC EFFECTS. Pregnancy Category C*

Albuterol sulfate: *Pregnancy Category C.* Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m² basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m² basis). Cleft palate formation also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Ipratropium bromide: *Pregnancy Category B.* Reproduction studies in CD-1 mice, Sprague-Dawley rats and New Zealand rabbits demonstrated no evidence of teratogenicity at oral doses up to 10, 100, and 125 mg/kg, respectively (approximately 15, 270, and 680 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). Reproduction studies in rats and rabbits demonstrated no evidence of teratogenicity at inhalation doses up to 1.5 and 1.8 mg/kg, respectively (approximately 4 and 10 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). There are no adequate and well-controlled studies of the use of DuoNeb, albuterol sulfate, or ipratropium bromide in pregnant women. DuoNeb should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery**

Oral albuterol sulfate has been shown to delay preterm labor in some reports. Because of the potential of albuterol to interfere with uterine contractility, use of DuoNeb during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

**Nursing Mothers**

It is not known whether the components of DuoNeb are excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken as a nebulized solution. Because of the potential for tumorigenicity shown for albuterol sulfate in some animals, a decision should be made whether to discontinue nursing or discontinue DuoNeb, taking into account the importance of the drug to the mother.

**Pediatric Use**

The safety and effectiveness of DuoNeb in patients below 18 years of age have not been established.

**Geriatric Use**

Of the total number of subjects in clinical studies of DuoNeb, 62 percent were 65 and over, while 19 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**ADVERSE REACTIONS**

Adverse reaction information concerning DuoNeb was derived from the 12-week controlled clinical trial.

**ADVERSE EVENTS OCCURRING IN ≥ 1% OF ≥ 1 TREATMENT GROUP(S) AND WHERE THE COMBINATION TREATMENT SHOWED THE HIGHEST PERCENTAGE**

| Body System<br>COSTART Term | Albuterol<br>n (%) | Ipratropium<br>n (%) | DuoNeb<br>n (%) |
|---|---|---|---|
| NUMBER OF PATIENTS | 761 | 754 | 765 |
| N (%) Patients with AE | 327 (43.0) | 329 (43.6) | 367 (48.0) |
| BODY AS A WHOLE | | | |
| Pain | 8 (1.1) | 4 (0.5) | 10 (1.3) |
| Pain chest | 11 (1.4) | 14 (1.9) | 20 (2.6) |
| DIGESTIVE | | | |
| Diarrhea | 5 (0.7) | 9 (1.2) | 14 (1.8) |
| Dyspepsia | 7 (0.9) | 8 (1.1) | 10 (1.3) |
| Nausea | 7 (0.9) | 6 (0.8) | 11 (1.4) |
| MUSCULO-SKELETAL | | | |
| Cramps leg | 8 (1.1) | 6 (0.8) | 11 (1.4) |
| RESPIRATORY | | | |
| Bronchitis | 11 (1.4) | 13 (1.7) | 13 (1.7) |
| Lung Disease | 36 (4.7) | 34 (4.5) | 49 (6.4) |
| Pharyngitis | 27 (3.5) | 27 (3.6) | 34 (4.4) |
| Pneumonia | 7 (0.9) | 8 (1.1) | 10 (1.3) |
| UROGENITAL | | | |
| Infection urinary tract | 3 (0.4) | 9 (1.2) | 12 (1.6) |

Additional adverse reactions reported in more than 1% of patients treated with DuoNeb included constipation and voice alterations.

In the clinical trial, there was a 0.3% incidence of possible allergic-type reactions, including skin rash, pruritus, and urticaria.

Additional information derived from the published literature on the use of albuterol sulfate and ipratropium bromide singly or in combination includes precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, paradoxical bronchospasm, wheezing, exacerbation of COPD symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, elevated heart rate, sinusitis, back pain and sore throat.

**DOSAGE AND ADMINISTRATION**

The recommended dose of DuoNeb is one 3 mL vial administered 4 times per day via nebulization with up to 2 additional 3 mL doses allowed per day, if needed. Safety and efficacy of additional doses or increased frequency of administration of DuoNeb beyond these guidelines has not been studied and the safety and efficacy of extra doses of albuterol sulfate or ipratropium bromide in addition to the recommended doses of DuoNeb have not been studied.

The use of DuoNeb can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of worsening COPD, which would require reassessment of therapy.

A Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONEB™ compressor was used to deliver DuoNeb to each patient in one U.S. clinical study. The safety and efficacy of DuoNeb delivered by other nebulizers and compressors have not been established.

DuoNeb should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.

**HOW SUPPLIED**

DuoNeb is supplied as a 3-mL sterile solution for nebulization in sterile low-density polyethylene unit-dose vials. Cards of five vials are placed into a foil pouch. Supplied in cartons as listed below:

NDC 49502-672-30 30 vials per carton
NDC 49502-672-60 60 vials per carton

Store between 2°C and 25°C (36°F and 77°F). Protect from light.

DEY, Napa, CA 94558

03-485-21(8RS) May 2001

1. Gross N, Tashkin D, Miller R, et al. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. *Respiration.* 1998;65:354-362.

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# CONTENTS

NOVEMBER 2001 / VOLUME 46 / NUMBER 11

## EVIDENCE-BASED MEDICINE IN RESPIRATORY CARE PART I

**A SPECIAL ISSUE**

CO-CHAIRS

Shelley C Mishoe PhD RRT FAARC
Dean R Hess PhD RRT FAARC

## CONFERENCE PROCEEDINGS

Foreword: Evidence-Based Medicine in Respiratory Care
*by Shelley C Mishoe—Augusta, Georgia and Dean R Hess—Boston, Massachusetts* 1200

What Is Evidence-Based Medicine and Why Should It Be Practiced?
*by Victor M Montori—Rochester, Minnesota and Gordon H Guyatt—Hamilton, Ontario, Canada* 1201

Outcomes Research in Respiratory Care
*by Robert L Chatburn—Cleveland, Ohio* 1215

From Data to Evidence: Evaluative Methods in Evidence-Based Medicine
*by Michel D Landry and William J Sibbald—Toronto, Ontario, Canada* 1226

Assessment of Health-Related Quality of Life
*by Shelley C Mishoe and J Ross Maclean—Augusta, Georgia* 1236

Translating Evidence into Practice: Pursuing Perfection in Pneumococcal Vaccination in a Rural Community
*by Daniel M Doyle, Robin Dauterive, Kenneth H Chuang, and A Gray Ellrodt—Pittsfield, Massachusetts* 1258

The Evidence for Secretion Clearance Techniques
*by Dean R Hess—Boston, Massachusetts* 1276

Chronic Obstructive Pulmonary Disease Management: The Evidence Base
*by Neil R MacIntyre—Durham, North Carolina* 1294

## LETTERS

The Future of Respiratory Care
*by Thomas L Petty—Denver, Colorado* 1304

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RESPIRATORY CARE

RESPIRATORY CARE (ISSN 0020-1324, USPS 0489-190) is published monthly by Daedalus Enterprises Inc, at 11030 Ables Lane, Dallas TX 75229-4593, for the American Association for Respiratory Care. One volume is published per year beginning each January. Subscription rates are $75 per year in the US, $90 in all other countries (for airmail, add $94).

The contents of the Journal are indexed in *Index Medicus*/MEDLINE, Hospital and Health Administration Index, Cumulative Index to Nursing and Allied Health Literature, EMBASE/Exerpta Medica, and RNdex Library Edition. Abridged versions of RESPIRATORY CARE are also published in Italian, French, and Japanese, with permission from Daedalus Enterprises Inc.

Periodicals postage paid at Dallas TX and at additional mailing offices. POSTMASTER: Send address changes to RESPIRATORY CARE, Membership Office, Daedalus Enterprises Inc, 11030 Ables Lane, Dallas TX 75229-4593.

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# CONTENTS

CONTINUED.

## ALSO IN THIS ISSUE


1317 AARC Membership Application

1178 Abstracts from Other Journals

1328 Advertisers Index & Help Lines

1328 Author Index

1325 Call for OPEN FORUM Abstracts

1314 Calendar of Events

1319 Manuscript Preparation Guide

1323 New Products

1324 Notices


## BOOKS, FILMS, TAPES, AND SOFTWARE


Decisions and Evidence in Medical Practice: Applying Evidence-Based Medicine to Clinical Decision Making (Gross R) 1305
*reviewed by Carin M Olson—Seattle, Washington*

Evidence-Based Medicine: How to Practice and Teach EBM, 2nd ed (Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB) 1306
*reviewed by Marcia L Edmonds—Edmonton, Alberta, Canada*

Introduction to Research in the Health Sciences, 4th ed (Polgar S, Thomas SA) 1307
*reviewed by Robert L Chatburn—Cleveland, Ohio*

Evidence-Based Asthma Management (Fitzgerald JM, Ernst P, Boulet L-P, O'Byrne PM) 1307
*reviewed by Harold J Farber and Barbara Langham—Vallejo, California*

Medicine Meets Virtual Reality 2000. Envisioning Healing: Interactive Technology and the Patient-Practitioner Dialogue (Westwood JD, Hoffman HM, Mogel GT, Robb RA, Stredney D, editors) 1309
*reviewed by Keith B Hopper—Marietta, Georgia*

Super Searchers on Health & Medicine: The Online Secrets of Top Health & Medical Researchers (Detwiler SM, Basch R, editors) 1309
*reviewed by Steven B Nelson—Overland Park, Kansas*


## RC WEB SITES


Evidence-Based Medicine: Online Resources 1311
*reviewed by Steven B Nelson—Overland Park, Kansas*


## CRCE THROUGH THE JOURNAL


2001 Answer Key 1327



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**Editorials, Commentaries, and Reviews to Note**

**Asthma: Prevalence, Pathogenesis, and Prospects for Novel Therapies**—Woodruff PG, Fahy JV. JAMA 2001;286(4):395–398.

**Exacerbations of Asthma: Still Room for Improvement**—Tattersfield AE, Harrison TW. Lancet 2001;358(9282):599–601.

**Treating Children with Asthma: A Review of Drug Therapies**—Kalister H. West J Med 2001;174(6):415–420.

**Sleep-Disordered Breathing in Children**—Marcus CL. Am J Respir Crit Care Med 2001; 164(1):16–30.

**Women with Cystic Fibrosis and Their Potential for Reproduction**—Edenborough FP. Thorax 2001;56(8):649–655.

**European Respiratory Society Guidelines on the Use of Nebulizers**—Boe J, Dennis JH, O'Driscoll BR, Bauer TT, Carone M, Dautzenberg B, et al, for the European Respiratory Society Task Force on the Use of Nebulizers. Eur Respir J 2001;18(1):228–242.

**When Should Clinical Guidelines Be Updated?**—Shekelle P, Eccles MP, Grimshaw JM, Woolf SH. BMJ 2001;323(7305):155–157.

**Ventilator-Associated Pneumonia. European Task Force on Ventilator-Associated Pneumonia**—Torres A, Carlet J. Eur Respir J 2001;17(5):1034–1045.

**Lethal Hemoptysis Caused by Biopsy Injury of an Abnormal Bronchial Artery**—Maxeiner H. Chest 2001;119(5):1612–1615.

A 62-year-old man with a long history of lung disease developed atelectasis of the right middle lung lobe, caused by a protrusion in the wall of the middle lobe bronchus. A biopsy was performed in the suspicious region. This was immediately followed by massive arterial bleeding into the airways and complicated by cardiac arrest soon after. The bleeding could not be controlled by nonsurgical treatment; the patient died 24 h after the complication because of pulmonary insufficiency. Autopsy revealed the bleeding to have been caused by a biopsy injury of a bronchial artery that had run superficially in the bronchial mucosa and had produced the intrabronchial protrusion. Several other abnormal intrabronchial arteries were found peripherally in this lung.

**Increasing Prevalence of Asthma Diagnosis and Symptoms in Children Is Confined to Mild Symptoms**—Ng Man Kwong G, Proctor A, Billings C, Duggan R, Das C, Whyte MK, et al. Thorax 2001;56(4):312–314.

BACKGROUND: The prevalence of childhood asthma is increasing but few studies have investigated trends in asthma severity. We investigated trends in asthma diagnosis and symptom morbidity between an eight year time period in a paired prevalence study. METHODS: All children in one single school year aged 8–9 years in the city of Sheffield were given a parent respondent questionnaire in 1991 and 1999 based on questions from the International Survey of Asthma and Allergy in Children (ISAAC). Data were obtained regarding the prevalence of asthma and wheeze and current (12 month) prevalences of wheeze attacks, speech limiting wheeze, nocturnal cough and wheeze, and exertional symptoms. RESULTS: The response rates in 1991 and 1999 were 4580/5321 (85.3%) and 5011/6021 (83.2%), respectively. There were significant increases between the two surveys in the prevalence of asthma ever (19.9% v 29.7%, mean difference 11.9%, 95% confidence interval (CI) 10.16 to 13.57, $p<0.001$), current asthma (10.3% v 13.0%, mean difference 2.7%, 95% CI 1.44 to 4.03, $p<0.001$), wheeze ever (30.3% v 35.8%, mean difference 5.7%, 95% CI 3.76 to 7.56, $p<0.001$), wheeze in the previous 12 months (17.0% v 19.4%, mean difference 2.5, 95% CI 0.95 to 4.07, $p<0.01$), and reporting of medication use (16.9% v 20%, mean difference 3.0%, 95% CI 1.46 to 4.62, $p<0.001$). There were also significant increases in reported hayfever and eczema diagnoses. CONCLUSIONS: Diagnostic labelling of asthma and lifetime prevalence of wheeze has increased. The current 12 month point prevalence of wheeze has increased but this is confined to occasional symptoms. The increased medication rate may be responsible for the static prevalence of severe asthma symptoms. The significant proportion of children receiving medication but reporting no asthma symptoms identified from our 1999 survey suggests that some children are being inappropriately treated or overtreated.

**Comparison of Physiological and Radiological Screening for Lung Volume Reduction Surgery**—Ingenito EP, Loring SH, Moy ML, Mentzer SJ, Swanson SJ, Hunsaker A, et al. Am J Respir Crit Care Med 2001;163(5):1068–1073.

Physiological and radiological criteria are both used to identify candidates for LVRS. This study compares the predictive value of these screening techniques among patients with homogeneous (Ho) and heterogeneous (He) emphysema. Preoperative inspiratory lung conductance ($G_{L_1}$) during spontaneous breathing and quantitative radioisotope V/Q scan (QVQS) results were available for 48 of 50 patients undergoing bilateral LVRS for emphysema. Ho disease (n = 21) was defined by QVQS as an upper/lower perfusion ratio (ULPR) between 0.75 and1.25. $G_{L_1}$ correlated with 6-mo improvement in $FEV_1$ ($\Delta FEV_1$-6) (r = 0.53, $p < 0.001$) for the entire cohort, and for patients with both Ho (n = 21, r = 0.56, p = 0.015) and He disease (n = 27, r = 0.46, p = 0.017). ULPR correlated less well with $\Delta FEV_1$-6 (n = 48, r = -0.38; p = 0.008) for the cohort, and was significantly correlated with outcomes only in the subgroup of patients with He disease (r = -0.40, p = 0.04). Multivariate regression demonstrated that by combining $G_{L_1}$ and ULPR criteria, 33% of the $\Delta FEV_1$-6 response could be accounted for. We conclude that both physiological and radiological criteria help identify appropriate candidates for LVRS. $G_{L_1}$ best identifies patients with Ho emphysema who may benefit from surgery, but would be excluded on the basis of strictly radiological criteria. ULPR helps identify patients with He disease that improves with surgery, despite unfavorable $G_{L_1}$.

**Psychopathology in Patients with Severe Asthma Is Associated with Increased Health Care Utilization**—ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Am J Respir Crit Care Med 2001;163(5):1093–1096.

Severe asthma accounts for the majority of health costs for this disease, which is mainly related to the treatment of failed control. Several psychosocial factors have been associated with poor asthma control, but the question remains whether psychiatric disorder in patients with severe asthma predisposes for increased health care utilization. In the present study we compared outpatients with severe asthma with and without psychological dysfunctioning with respect to health care utilization. All patients used high dose inhaled corticosteroids and long-acting bronchodilators for more than 1 yr, and had difficult-to-control asthma, requiring one or more courses of corticosteroids during the past year or maintenance therapy with prednisone. Medical history was taken and health care utilization questionnaires were completed. The General Health Questionnaire (GHQ) was used to identify psychiatric cases (GHQ-12 score of ≥ 6). There were no differences between the psychiatric cases (n = 21) and the noncases (n = 77) with respect to demographic and objective disease characteristics. However, the psychiatric cases had increased odds ratios (OR) for frequent visits to GP (OR = 5.9), frequent emergency visits (OR = 5.3), frequent exacerbations (OR = 12.4), and frequent hospitalizations (OR = 4.8) as compared with the nonpsychiatric patients. The present findings suggest that the morbidity and costs of asthma might be related to the level of psychological dysfunctioning in patients with severe asthma rather than to asthma severity per se, thereby identifying an area of potential intervention.

**Breathing He-$O_2$ Increases Ventilation But Does Not Decrease the Work of Breathing During Exercise**—Babb TG. Am J Respir Crit Care Med 2001;163(5):1128–1134.

We previously observed an increase in minute ventilation ($\dot{V}_E$) with resistive unloading (He-O2 breathing) in healthy elderly subjects with normal pulmonary function. To investigate the effects of resistive unloading in elderly subjects with mild chronic airflow limitation ($FEV_1$/FVC: 61 ± 4%), we studied 10 elderly men and women 70 ± 3 yr of age. These subjects performed graded cycle ergometry to exhaustion, once breathing room air and once breathing a He-$O_2$ gas mixture (79% He, 21% $O_2$). $\dot{V}_E$, pulmonary mechanics, and $PET_{CO_2}$ were measured during each 1-min increment in work rate. Data were analyzed by paired t test at rest, at ventilatory threshold (VTh), and during maximal exercise. $\dot{V}_I$ was significantly ($p < 0.05$) increased at VTh (3.4 ± 4.0 L/min or 12 ± 15% increase) and maximal exercise (15.2 ± 9.7 L/min or 22 ± 13% increase) while breathing He-$O_2$. Concomitant to the increase in $\dot{V}_E$, $PET_{CO_2}$ was decreased at all levels ($p < 0.01$), whereas total work of breathing against the lung was not different. We concluded that $\dot{V}_E$ is increased during He-$O_2$ breathing because of resistive unloading of the airways and the maintenance of the relationship between the work of breathing and exercise work rate.

**Exhaled and Nasal Nitric Oxide As a Marker of Pneumonia in Ventilated Patients**—Adrie C, Monchi M, Dinh-Xuan AT, Dall'Ava-Santucci J, Dhainaut JF, Pinsky MR. Am J Respir Crit Care Med 2001; 163(5):1143–1149.

Because inflammation stimulates the expression of inducible nitric oxide (NO) synthase (iNOS) with an associated increased local NO production, we hypothesized that patients with pneumonia would have increased excretion of NO into their airways. To test this hypothesis, NO was measured in the exhaled air and from the nasal cavities of 49 consecutively intubated and mechanically ventilated patients in our ICU. After excluding NO gas contamination in the inspiratory circuit, nasal NO and end-expiratory and mean exhaled tracheal NO levels and plasma nitrate concentrations were measured using a fast response chemiluminescence analyzer. Twenty-one patients (43%) presented with infectious pneumonia. End- expiratory exhaled NO concentrations were significantly higher in patients with pneumonia as compared with patients without pneumonia (5.9 ± 1 ppb versus 3.2 ± 0.5 ppb, $p < 0.01$). Similarly, mean nasal NO was higher in patients with pneumonia (1039 ± 138 ppb versus 367 ± 58 ppb, p = 0.003). Plasma nitrate levels did not differ between patient groups. Threshold values of tracheal or nasal NO were defined and subsequently validated in 60 other patients. Positive and negative values of a maximal tracheal level > 5 ppb for pneumonia were 74% and 89%,


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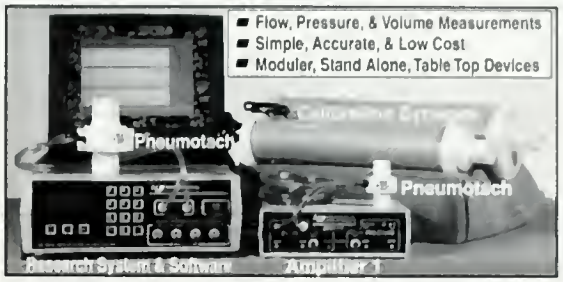


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respectively. Thus tracheal and nasal NO levels may be of help in distinguishing patients with acute pneumonia from other causes. Furthermore, because these differences in airway NO levels were not paralleled in blood nitrite concentrations, we conclude that pneumonia per se is not associated with systemic NO production.

**Production of Inflammatory Cytokines in Ventilator-Induced Lung Injury: A Reappraisal**—Ricard JD, Dreyfuss D, Saumon G. Am J Respir Crit Care Med 2001;163(5):1176–1180.

We investigated the production of proinflammatory cytokines by the lung during high mechanical stretch in vivo. To do this, we subjected rats to high-volume (42 mL/kg tidal volume [$V_T$]) ventilation for 2 h. The animals developed severe pulmonary edema and alveolar flooding, with a high protein concentration in bronchoalveolar lavage fluid (BALF). The animals' BALF contained no tumor necrosis factor (TNF)-$\alpha$, negligible amounts of interleukin (IL)-1$\beta$, and less than 300 pg/mL of the chemokine macrophage inflammatory protein (MIP)-2, an amount similar to that found in rats ventilated with 7 mL/kg $V_T$. Systemic cytokine levels were below the detection threshold. Because isolated lungs have been shown to produce high levels of proinflammatory cytokines when ventilated with a similarly high $V_T$ for the same duration (Tremblay, et al. J Clin Invest 1997;99:944–952), we reconsidered this specific issue. We ventilated isolated, unperfused rat lungs for 2 h with 7 mL/kg or 42 mL/kg $V_T$, or maintained them in a statically inflated state. Negligible amounts of TNF-$\alpha$ were found in the BALF whatever the ventilatory condition applied. The BALF IL-1$\beta$ concentration was slightly elevated and higher in lungs ventilated with 42 mL/kg $V_T$ than in those ventilated with 7 mL/kg $V_T$ or in statically inflated lungs ($p < 0.05$). The BALF MIP-2 concentration was moderately elevated in all isolated lungs (200 to 300 pg/mL), and was slightly higher ($p < 0.05$) in lungs ventilated with 42 mL/kg $V_T$. After lipopolysaccharide (LPS) challenge, high levels of TNF-$\alpha$, IL-1$\beta$, and MIP-2 were found in the animals' plasma before the lungs were removed. Negligible amounts of TNF-$\alpha$ and IL-1$\beta$ were retrieved from the BALF of statically inflated lungs. The concentrations of TNF-$\alpha$ and IL-1$\beta$ were higher in the BALF of ventilated lungs ($p < 0.001$). The TNF-$\alpha$ level did not differ with the magnitude of $V_T$, whereas the level of IL-1$\beta$ was significantly higher in BALF of lungs ventilated with 42 mL/kg $V_T$ ($p < 0.01$). The MIP-2 concentrations were similar for the two ventilatory conditions. These results suggest that ventilation that severely injures lungs does not lead to the release of significant amounts of TNF-$\alpha$ or IL-1$\beta$ by the lung in the absence of LPS challenge but may increase lung MIP-2 production.

**Chemical Control Stability in Patients with Obstructive Sleep Apnea**—Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Am J Respir Crit Care Med 2001;163(5):1181–1190.

The role of chemical control instability in the pathogenesis of obstructive sleep apnea (OSA) is not clear. We studied 32 patients with OSA during sleep while their upper airway was stabilized with continuous positive airway pressure. Twelve patients had repetitive OSA whenever they were asleep, regardless of body position or sleep stage, and were classified as having severe OSA (apnea-hypopnea index [AHI] = 88 ± 19). The remaining 20 patients had sporadic OSA or repetitive OSA for only part of the time (mild/moderate OSA; AHI = 27 ± 16). Susceptibility to periodic breathing (PB) was assessed by gradually increasing controller gain, using proportional assist ventilation. The increase in loop gain (LG) at each assist level was quantified from the ratio of assisted tidal volume ($V_T$) to the $V_T$ obtained during single-breath reloading tests ($V_T$ amplification factor [$V_{TAF}$]). Nine of 12 patients with severe OSA developed PB, with recurrent central apneas, whereas only six of 20 patients in the mild/moderate group developed PB ($p < 0.02$). This difference was observed despite the subjection of the mild/moderate group to greater amplification of LG; the highest values of $V_{TAF}$ in the mild/moderate and severe groups were 2.7 ± 1.0 and 1.9 ± 0.7, respectively ($p < 0.01$). We conclude that the chemical control system is more unstable in patients with severe OSA than in patients with milder OSA. We speculate that this may contribute to the severity of OSA, at least in some patients.

**How Accurate Are Pulse Oximeters in Patients with Acute Exacerbations of Chronic Obstructive Airways Disease?**—Kelly AM, McAlpine R, Kyle E. Respir Med 2001;95(5):336–340.

The aim of this study was to determine the extent of correlation and agreement between arterial oxygen saturation and oxygen saturation as recorded by transcutaneous pulse oximetry, with a view to identifying whether pulse oximetry can be used as an alternative to arterial values in the clinical management of patients with acute exacerbations of chronic obstructive airways disease (COAD) in the emergency department. It also aims to determine whether there is a cut-off level of oxygen saturation by pulse oximetry that can screen for significant systemic hypoxia in this group. This prospective study of patients with acute exacerbations of COAD who were deemed by their treating doctor to require an arterial blood gas analysis to determine their ventilatory status, compared arterial oxygen saturation with simultaneously recorded oxygen saturation measured by transcutaneous pulse oximetry. Data were analysed using Pearson correlation, bias plot (Bland-Altman) methods for agreement and the receiver operator characteristic (ROC) curve method for determination of a screening cut-off. Sixty-four sample-pairs were analysed for this study. Nine (14%) had significant hypoxia (arterial $P_{O_2}$ less than 60 mm Hg). The correlation coefficient was 0.91. The bias (Bland-Altman) plot shows a constant bias of -0.758% and only fair agreement, with 95% limits for agreement of -8.2 to + 6.7%. With respect to the ROC curve analysis, the best cut-off for detection of hypoxia was at oxygen saturation by pulse oximetry of 92% (sensitivity 100%, specificity 86%). In conclusion, there is not sufficient agreement for oxygen saturation measured by pulse oximetry to replace analysis of an arterial blood gas sample in the clinical evaluation of oxygenation in emergency patients with COAD. However, oxygen saturation by pulse oximetry may be an effective screening test for systemic hypoxia, with the screening cut-off of 92% having sensitivity for the detection of systemic hypoxia of 100% with specificity of 86%.

**Asthma and Gastro-Oesophageal Reflux: Can the Response to Anti-Reflux Therapy Be Predicted?**—Kiljander T, Salomaa ER, Hietanen E, Helenius H, Liippo K, Terho EO. Respir Med 2001;95(5):387–392.

The aim of the study was to investigate which features predict favourable response to omeprazole therapy in asthmatics with gastro-oesophageal reflux (GER). The study population consisted of 52 outpatient asthmatics with GER who had completed an intervention where they were randomized to receive omeprazole 40 mg once a day or placebo for 8 weeks. After a 2-week washout period the patients were crossed over. Asthma symptoms were found to be relieved ≥ 20% in 18 (35%) patients who were thus regarded as responders. A logistic regression analysis was performed in order to identify which features separate the responders from the non-responders. More responders were found among the patients whose body mass index (BMI) was higher ($p = 0.02$) or whose distal esophageal reflux was more severe [total time (%) pH < 4 ($p = 0.01$) or time (%) pH < 4 in upright position ($p = 0.04$)]. Adding other predictors to the total time (%) pH < 4, which was the most significant predictor for response in multi-variate analysis, did not further increase the prediction for favourable outcome. It is concluded that severe distal oesophageal reflux and obesity predict amelioration in asthma symptoms after 8-week omeprazole treatment in asthmatics with GER. Adding more than one predictor does not seem to further increase prediction for favourable asthma response.

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**Optimal Continuous Positive Airway Pressure in Patients with Obstructive Sleep Apnoea: Role of Craniofacial Structure**—Akashiba T, Kosaka N, Yamamoto H, Ito D, Saito O, Horie T. Respir Med 2001; 95(5):393–397.

Although nasal continuous positive airway pressure (CPAP) is effective in improving nocturnal obstructive apnoea, daytime sleepiness and well-being in patients with obstructive sleep apnoea syndrome (OSAS), not all patients tolerate this treatment. Since optimal CPAP titration is essential to maintain compliance, it is important to elucidate the factors that help to determine the optimal pressure. However, the determinants of the optimal CPAP level are controversial. The subjects comprised 27 Japanese male patients with OSAS who underwent standard polysomnography (PSG), pulmonary function tests, arterial blood gas analysis, cephalometry and CPAP titration. Twenty normal controls also underwent cephalometric analysis. The apnoea-hypopnoea index (AHI), mean oxygen saturation (mean $S_{aO_2}$) and the lowest $S_{aO_2}$ during sleep were found to be 54.7±22.6, 89.0±5.6%, and 69.7±9.0%, respectively by PSG. The mean optimal CPAP was 9.6±1.8 cm $H_2O$. The cephalometric angles (SNA, SNB and NSBa) were similar to those found in the control subjects, but MP-H, and PNS-P were significantly longer than those in the control subjects as shown by cephalometry. The optimal CPAP was correlated with the mean $S_{aO_2}$ ($p<0.0001$), neck circumference ($p<0.05$) and three cephalometric variables (NSBa: $p<0.01$, MP-H: $p<0.05$, PNS-P: $p<0.05$). Multiple, step-wise, regression analysis showed that the mean $S_{aO_2}$ and NSBa were independent variables that best predicted the optimal CPAP. These variables accounted for 57.5% of the total variance ($R^2=0.575$, $p<0.001$). Optimal CPAP was closely correlated with oxygen desaturation during sleep. However, the craniofacial structure had additional effects such as an independent factor in determining the optimal CPAP level.

**Has the Perception of Disability Among COPD Patients Applying for Pension Changed During the Last 20 Years?**—Ringbaek T, Viskum K. Respir Med 2001;95(5):398–403.

The aim is to examine the change in lung function, treatment and pulmonary symptoms in patients with chronic obstructive pulmonary disease (COPD) or chronic bronchitis (CB) applying for a pension during the period 1977–1996. In addition, we compared the perception of disability in males and females. From 1977 to 1996, 947 patients with COPD or CB were evaluated for obtaining economic support due to disability. In order to test the trend, the patients were divided into three periods: (1) 1977–1983, (2) 1984–1989 and (3) 1990–1996. Compared to females, males had substantial more pack-years of smoking (36 vs. 28, $p<0.001$), but their $FEV_1$ was only slightly decreased (46.9% versus 49.6% predicted, $p=0.047$). Females reported significantly more often attacks of dyspnoea [OR: 1.5(1.00–2.2)] and any kind of dyspnoea during daytime [OR: 4.0(1.2–13.3)]. From period 1 to period 3, $FEV_1$ increased significantly (45–53% predicted, $p<0.001$). Despite the increased $FEV_1$, the use of inhaled corticosteroid had increased markedly (9–32% of the patients, $p<0.001$). The results did not change when patients with asthma were included. Our data suggest that both sexes, especially females, have become more aware of pulmonary symptoms and tend to react to them more actively by demanding evaluation and treatment.

**Compliance with Inhaled Glucocorticoids and Concomitant Use of Long-Acting $\beta_2$-Agonists**—van der Woude HJ, Aalbers R. Respir Med 2001;95(5):404–407.

We investigated whether treatment with a long-acting $\beta_2$-agonist ($LA\beta_2$) is associated with a decrease in patient compliance with regard to inhalation corticosteroids (ICS). Date on prescriptions collected by 15,760 patients suffering from airways disease were provided by 69 Dutch pharmacies. All prescriptions of ICS and $LA\beta_2$ were analysed and divided in four groups by $LA\beta_2$ use during 1997 and 1998. Date from 15,760 patients were available. In the 10,929 patients not treated with $LA\beta_2$, compliance decreased slightly but not significantly. In 3281 patients receiving $LA\beta_2$ compliance also decreased slightly but not significantly. In 404 patients, who used a $LA\beta_2$ in 1997 and discontinued treatment in 1998, the compliance fell significantly ($p<0.05$). In 1147 patients who started to use a $LA\beta_2$ in 1998, compliance with ICS significantly improved ($p<0.05$). These results suggest that the regular use of $LA\beta_2$ improves compliance with ICS. Therefore, the concern that compliance with inhaled corticosteroid therapy will decrease under concomitant use of $LA\beta_2$ appear to be unfounded.

**Diagostic Value of Respiratory Impedance Measurements in Elderly Subjects**—Janssens JP, Nguyen MC, Herrmann FR, Michel JP. Respir Med 2001;95(5):415–422.

Obstructive lung disease (OLD) is highly prevalent in elderly subjects but markedly under-diagnosed. Indeed, only 40–50% of hospitalized elderly patients are able to adequately perform spirometric tests. This study aimed to evaluate, in an acute-care geriatric hospital, the diagnostic value of measuring airway impedance (Zrs) by the forced oscillation technique (FOT) for: (1) identifying OLD and (2) identifying responders vs. non-responders to bronchodilators. Sixty-seven patients (aged 82±8 years) underwent consecutive measurement of Zrs and forced expiratory volumes before and after bronchodilators. Zrs was measured by FOT at frequencies of 4–30 Hz. Correlations, ROC curves and logistic regression models were established to determine the sensitivity (Se) and specificity (Sp) of Zrs in identifying OLD. Significant correlations were found between spirometric and Zrs measurements. The Zrs parameters yielding the best Se and Sp for detecting OLD were: Fn (resonant frequency; Se: 76%; Sp: 78%) and R0 (resistance extrapolated for a frequency of 0; Se: 76%; Sp: 74%). Using the logistic regression models, 76% of the patients were correctly classified as having OLD or not. Zrs was however not contributive in identifying responders to bronchodilators. Zrs measurements by FOT are contributive to the diagnosis of OLD in elderly hospitalized patients.

**Symptoms Related to Obstructive Sleep Apnoea Are Common in Subjects with Asthma, Chronic Bronchitis and Rhinitis in a General Population**—Larsson LG, Lindberg A, Franklin KA, Lundback B. Respir Med 2001;95(5):423–429.

The purpose of this study was to examine the prevalence of self-reported snoring, apnoeas and daytime sleepiness in relation to chronic bronchitis, recurrent wheeze, physician-diagnosed asthma and rhinitis. This was a questionnaire study in a representative sample of a general population. The study was a part of the Obstructive Lung Disease in Northern Sweden Studies (OLIN). A total of 5424 subjects aged 20–69 years, born on the 15th day of each month, participated in the study. Eligible answers were obtained from 4648 subjects (85.7%). Having snoring as a problem was reported by 10.7%. Among subjects with chronic bronchitis it was reported by 25.9%, with recurrent wheeze by 21.3%, with physician-diagnosed asthma by 17.9%, and with rhinitis by 14.7%. Relatives' concerns of witnessed apnoea was reported by 6.8% of all subjects, while among subjects with chronic bronchitis it was reported by 18.1%, with recurrent wheeze by 17.1%, with physician-diagnosed asthma by 14.3%, and with rhinitis by 9.1%. After correction for age, gender and smoking habits, chronic bronchitis, rhinitis, asthma, and current smoking were significantly related, with snoring as a problem and with relatives' concern of witnessed apnoeas. Symptoms of daytime sleepiness were significantly related with concern of witnessed apnoeas, chronic bronchitis, snoring as a problem, recurrent wheeze and age 50–59 years. In conclusion, respiratory symptoms and conditions affecting mainly the lower respiratory tract, such as chronic bronchitis and asthma, were related with symptoms common in obstructive sleep apnoea.

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**Quality of Life in Survivors of Prolonged Mechanical Ventilatory Support**—Chatila W, Kreimer DT, Criner GJ. Crit Care Med 2001; 29(4):737–742.

OBJECTIVE: To examine the long-term quality of life (QOL) in a group of patients after prolonged mechanical ventilatory support. DESIGN: Prospective cohort study. SETTING: Outpatient follow-up. PATIENTS: Survivors of prolonged mechanical ventilatory support who were discharged from a ventilator rehabilitation unit (VRU). INTERVENTIONS: Measurement of health-related QOL using the Sickness Impact Profile (SIP). MEASUREMENTS AND MAIN RESULTS: Forty-six patients were contacted approximately 2 yrs after their discharge from the VRU and asked to complete the SIP. Twenty-five patients (age, 59 ± 17 yrs; duration of mechanical ventilatory support, 45 ± 36 days [mean ± sd]) agreed to participate in this study and completed the SIP questionnaire 23 ± 18 months after their discharge from the VRU. Patients' VRU stay was 29 ± 21 days. Two patients were discharged with nocturnal ventilatory support, and the rest were completely weaned of mechanical ventilatory support before discharge. Fifteen patients (60%) were discharged to home, eight patients (32%) were discharged to a rehabilitation facility, and two patients (8%) were discharged to a skilled-care facility. Most patients had mild dysfunction, and the global SIP score was 12 ± 10, the physical dimension score was 12 ± 12, and the psychosocial dimension score was 9 ± 11. (SIP scores range from 0 to 100, with higher scores indicating worse QOL.) Subgroup analysis showed that postoperative patients had lower SIP scores compared with patients with chronic respiratory diseases (global SIP, 7 ± 6 vs. 19 ± 8; $p < 0.05$). Moreover, the patients in the postoperative group were older, but had similar SIP scores as patients who had acute lung injury (17 ± 15). Global SIP scores correlated with age ($r = -0.40$; $p = 0.046$), but not with duration of mechanical ventilatory support ($r = -0.23$) or VRU admission Acute Physiology and Chronic Health Evaluation II scores ($r = -0.39$; $p = 0.06$). CONCLUSIONS: In survivors of prolonged mechanical ventilatory support, using specific selection criteria shows that there is minimal impairment in the QOL at long-term follow-up. Although some patients continue to have moderate to severe limitations, it is the cause of respiratory failure and the underlying disease, rather than duration of ventilatory support, that have a significant impact on QOL.

**Intensive Care Unit Physician Staffing Is Associated with Decreased Length of Stay, Hospital Cost, and Complications After Esophageal Resection**—Dimick JB, Pronovost PJ, Heitmiller RF, Lipsett PA. Crit Care Med 2001;29(4):753–758.

OBJECTIVE: To determine whether having daily rounds by an intensive care unit (ICU) physician is associated with clinical and economic outcomes after esophageal resection. DESIGN: ICU information was obtained from a prospective survey and linked to retrospective patient data from the Maryland Health Services Cost Review Commission. The main outcome variables were in-hospital mortality rate, length of stay, hospital cost, and complications after esophageal resection. SETTING: Nonfederal acute care hospitals in Maryland that performed esophageal resection ($n = 35$ hospitals) during the study period, 1994–1998. PATIENTS: Adult patients who underwent esophageal resection in Maryland ($n = 366$ patients) from 1994 to 1998. INTERVENTIONS: Presence vs. absence of daily rounds by an ICU physician. MEASUREMENTS AND MAIN RESULTS: After adjusting for patient case-mix and other hospital characteristics, lack of daily rounds by an ICU physician was independently associated with a 73% increase in hospital length of stay (7 days; 95% confidence interval [CI], 1–15; $p = 0.012$) and a 61% increase in total hospital cost ($8,839; 95% CI, $ 1,674-$19,192; $p = 0.013$), but there was no association with in-hospital mortality rate. In addition, the following postoperative complications were independently associated with lack of daily rounds by an ICU physician: pulmonary insufficiency (odds ratio [OR], 4.0; CI, 1.4–11.0), renal failure (OR, 6.3; CI, 1.4–28.7), aspiration (OR, 1.7; CI, 1.0–2.8), and reintubation (OR, 2.8; CI, 1.5–5.2). CONCLUSIONS: Having daily rounds by an ICU physician is associated with shorter lengths of stay, lower hospital cost, and decreased frequency of postoperative complications after esophageal resection. Healthcare providers and policymakers should use this information to help improve quality of care and reduce costs for patients undergoing high-risk surgical procedures.

**Pupil Diameter and Light Reaction During Cardiac Arrest and Resuscitation**—Zhao D, Weil MH, Tang W, Klouche K, Wann SR. Crit Care Med 2001;29(4):825–828.

OBJECTIVE: Traditionally, both pupil diameter and reaction to light have been examined to confirm the diagnosis of death. In the present study, we investigated quantitative changes in pupil diameter and light reaction for assessing the efficacy of cardiopulmonary resuscitation (CPR) and as a predictor of outcome. DESIGN: Controlled experimental study. SETTING: Animal research laboratory at a university-affiliated research institute. SUBJECTS: Fifteen domestic male pigs weighing between 33 and 40 kg. INTERVENTIONS: Ventricular fibrillation was induced with an alternating current delivered to the right ventricular endocardium. After 7 mins of untreated ventricular fibrillation, chest compression and mechanical ventilation were initiated and maintained for 6 mins. Restoration of spontaneous circulation then was attempted by electrical defibrillation. MEASUREMENTS AND MAIN RESULTS: Spontaneous circulation was reestablished in 9 of 15 animals. Pupils were fully dilated, and pupillary reaction to light was absent in 7 of the 9 resuscitated animals during untreated cardiac arrest. Progressive decreases in pupil diameter were observed together with restoration of light reaction during CPR, in each animal that was successfully resuscitated. When the pupils remained dilated and unreactive after 6 mins of CPR, resuscitation efforts were uniformly unsuccessful. A highly significant linear correlation between coronary perfusion pressure generated during precordial compression and pupil diameter was documented. Both were predictive of outcome. CONCLUSIONS: Dynamic changes of pupil diameter and reactions to light during cardiac arrest and resuscitation were correlated with coronary perfusion pressure, and both predicted the likelihood that spontaneous circulation and cerebral function would be restored.

**Successful Extracorporeal Life Support in a Case of Severe Flecainide Intoxication**—Auzinger GM, Scheinkestel CD. Crit Care Med 2001; 29(4):887–890.

OBJECTIVE: To show the effectiveness of emergency extracorporeal membrane oxygenation (ECMO) in treating severe, life-threatening flecainide intoxication. DESIGN: Case report. SETTING: Intensive care unit in a quaternary care center. PATIENT: A patient with electromechanical dissociation after severe flecainide acetate overdose. INTERVENTION: ECMO. CASE REPORT: A 30-yr-old male with a history of depression presented after a severe flecainide overdose with plasma concentrations exceeding 20 times the upper boundary of the therapeutic range. At presentation, the patient was in refractory cardiocirculatory collapse and was successfully resuscitated with ECMO. Twenty-six hours later, extracorporeal support could be discontinued and the patient made a full recovery. CONCLUSION: In patients with severe but potentially reversible cardiac dysfunction attributable to flecainide intoxication, ECMO can maintain cardiac output and vital organ perfusion while allowing time for drug redistribution, metabolism, and clearance.

**In-Hospital and Long-Term Prognosis of Elderly Patients Requiring Endotracheal intubation for Life-Threatening Presentation of Cardiogenic Pulmonary Edema**—Adnet F, Le Toumelin P, Leberre A, Minadeo J, Lapostolle F, Plaisance P, Cupa M. Crit Care Med 2001; 29(4):891–895.

OBJECTIVE: We studied the in-hospital course, long-term prognosis, and functional status of elderly patients with life-threatening cardiogenic pulmonary edema requiring mechanical ventilation. DESIGN: Semiprospective evaluation. SETTING: Twelve intensive care units and one emergency prehospital medical department in university hospitals. PATIENTS: Patients, aged >75 yrs, with life-threatening cardiogenic pulmonary edema requiring invasive airway management during the prehospital phase between January 1994 and January 1999 were included. INTERVENTION: None. MEASUREMENTS AND MAIN RESULTS: A total of 79 patients were studied, of which 55 were included in the prospective phase and 24 during the retrospective phase. The age range was 75–99 yrs, with a mean age of 82.4 ± 5.9. The male/female ratio was 35:44. The in-hospital mortality was 26.6%. The mean follow-up time for all 58 survivors was 23 months (range, 2–56 months). Among those discharged, survival at 1 yr was 69%. At 3 months after hospital discharge, 49 (87%) patients lived at home, 46 (82%) were able to bathe themselves, 35 (62%) could walk at least one block, and 34 (61%) could climb one flight of stairs. CONCLUSIONS: Mortality after severe pulmonary edema requiring endotracheal intubation in a very elderly cohort has a predictably high mortality, although not related directly to the degree of presenting respiratory compromise. However, approximately 50% of the overall cohort returned to relatively good functional status, despite advanced age and a severely compromised presentation. Aggressive airway management appears, therefore, justified in this select group of patients.

**New Bronchoscopic Microsample Probe to Measure the Biochemical Constituents in Epithelial Lining Fluid of Patients with Acute Respiratory Distress Syndrome**—Ishizaka A, Watanabe M, Yamashita T, Ogawa Y, Koh H, Hasegawa N, et al. Crit Care Med 2001;29(4):896–898.

OBJECTIVE: A noninvasive bronchoscopic microsampling (BMS) probe was developed to sample biochemical constituents of the epithelial lining fluid in small airways. DESIGN: Observational, controlled study. SETTING: Intensive care unit of academic medical center. PATIENTS AND PROCEDURE: BMS was applied in a control group of seven patients who had hemoptysis or small solitary peripheral nodules but no hypoxemia or other signs of acute inflammation and in four patients with acute respiratory distress syndrome (ARDS), to test whether BMS can ascertain the presence of acute pulmonary inflammation without complications. MEASUREMENTS AND RESULTS: Complications, including a significant decrease in arterial oxygen saturation, were observed neither during nor after BMS. In the ARDS group, albumin, lactate dehydrogenase, interleukin-6, basic fibroblast growth factor, and neutrophil elastase concentrations in epithelial lining fluid were significantly higher ($p < 0.0001$, $p = 0.012$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively) than in the control group. Serial BMS was safely performed in one patient with ARDS, allowing us to observe a correlation between changes in the concentration of inflammation-related biochemical markers and clinical course of the disease. CONCLUSIONS: These results suggest that BMS is safe and useful to monitor pulmonary biochemical events in ARDS.

**Infection Control Measures to Limit Antimicrobial Resistance**—Warren DK, Fraser VJ. Crit Care Med 2001;29(4 Suppl):N128-N134.

Increasing antimicrobial resistance has resulted in a rapidly decreasing array of therapeutic options for infections in the critical care setting. Reports of reduced susceptibility to vancomycin in *Staphylococcus aureus* raise the possibility of patients being infected with a virulent pathogen for which most antibiotics are ineffective. Infection control methods to contain resistance, exclusive of antimicrobial restrictions, focus on surveillance to identify carriers of resistant organisms, prevention of nosocomial infections, adequate hand hygiene, isolation of patients who harbor resistant organisms, and the use of barrier techniques such as


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gowns and gloves. Surveillance using clinical isolates alone is inadequate for the identification of the majority of patients who carry resistant organisms. However, it is unclear what intensity of surveillance is needed to control the spread of these organisms in the intensive care unit in nonoutbreak situations. Attempts at eradicating carriage are often unsuccessful when there is extranasal colonization with methicillin-resistant *S. aureus*. Transmission of resistant organisms is primarily the result of transient contamination of healthcare workers' hands. Adequate handwashing, isolation of carriers, and barrier techniques are all necessary for containing resistance within the intensive care unit, however, compliance with these measures can be compromised by high staff turnover and heavy workload.

**Impact of Antibiotic Resistance on Clinical Outcomes and the Cost of Care**—Niederman MS. Crit Care Med 2001;29(4 Suppl):N114-N120.

Antibiotic-resistant organisms are common in intensive care unit infection and can be either Gram-positive or Gram-negative. A number of studies have evaluated whether these organisms can lead to excess morbidity, mortality, or cost. In general, the studies are confounded by a number of methodologic issues, including the selection of an appropriate control population. Cases and controls must be appropriately matched for the presence of infection, the presence of infection with similar organisms (but ones that are either antibiotic-sensitive or -resistant), and severity of illness. In addition, studies must account for the therapies given to patients who are infected with resistant organisms because resistance is an important risk factor for inadequate empirical therapy, and such therapy is itself a potent determinant of a number of adverse outcomes, including mortality. To date, the data with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus are inconsistent with regard to the effect on mortality rates, although infection with both organisms can lead to excess length of stay and increased cost of care. When studies have been adequately controlled and powered, infection with vancomycin-resistant enterococcus has had more of an effect on the mortality rate than infection with antibiotic-sensitive enterococci. Infection with resistant Gram-negatives also has adverse impact on outcome, with excess mortality being seen in patient groups infected with Acinetobacter and *Pseudomonas aeruginosa*. If we are to minimize the effect of resistance on medical outcomes and cost, it will be necessary to have a current knowledge of each intensive care unit's pathogens and susceptibility patterns, so that empirical therapy will have a good likelihood of being effective. In addition, new therapeutic agents may improve on the efficacy of older agents and could reduce cost if they allow for some patients to leave the hospital and to finish therapy with an oral formulation of a highly bioavailable agent.

**Improving Interpretation of Clinical Studies by Use of Confidence Levels, Clinical Significance Curves, and Risk-Benefit Contours**—Shakespeare TP, Gebski VJ, Veness MJ, Simes J. Lancet 2001;357(9265):1349–1353.

The process of interpreting the results of clinical studies and translating them into clinical practice is being debated. Here we examine the role of p values and confidence intervals in clinical decision-making, and draw attention to confusion in their interpretation. To improve result reporting, we propose the use of confidence levels and plotting of clinical significance curves and risk-benefit contours. These curves and contours provide degrees of probability of both the potential benefit of treatment and the detriment due to toxicity. Additionally, they provide clinicians with a mechanism of translating the results of studies into treatment for individual patients, thus improving the clinical decision-making process. We illustrate the application of these curves and contours by reference to published studies. Confidence levels, clinical significance curves, and risk-benefit contours can be easily calculated with a hand calculator or standard statistical packages. We advocate their incorporation into the published results of clinical studies.

**Computerised Tomography Scan Imaging in Acute Respiratory Distress Syndrome**—Pesenti A, Tagliabue P, Patroniti N, Fumagalli R. Intensive Care Med 2001;27(4):631–639.

Computerised tomography (CT) is being used with increasing frequency in acute respiratory distress syndrome (ARDS) patients. This brief review will discuss some of the clinical insights that a CT scan can offer. A large number of CT scan studies have provided new insights into the pathophysiology of ARDS and of mechanical ventilation, and are particularly focused on the recruitment-derecruitment phenomenon. To this end, newer fast CT scan technology promises a dynamic, rather than a static view of lung ventilation.

**Usefulness of a Strategy Based on Bronchoscopy with Direct Examination of Bronchoalveolar Lavage Fluid in the Initial Antibiotic Therapy of Suspected Ventilator-Associated Pneumonia**—Timsit JF, Cheval C, Gachot B, Bruneel F, Wolff M, Carlet J, Regnier B. Intensive Care Med 2001;27(4):640–647.

OBJECTIVES: To evaluate (a) the routine accuracy of bronchoalveolar lavage by direct examination (BAL-D) in diagnosing ventilator-associated pneumonia (VAP), and (b) the impact of a diagnostic strategy including clinical judgment, bronchoscopy, and BAL-D on the initial diagnosis and appropriateness of treatment when VAP is suspected. DESIGN AND SETTING: Prospective cohort study in two academic ICUs in Paris, France. PATIENTS AND PARTICIPANTS: Mechanically ventilated patients with suspected VAP underwent bronchoscopy with BAL and protected specimen brush (PSB). BAL-D results were available within 2 h, BAL on culture and PSB results after 24 h, and antibiotic susceptibility after 48 h. At each step in the strategy the senior and the resident in charge of the patient were asked their diagnosis and their therapeutic plan on the basis of presently available data. Definite diagnosis of suspected VAP was based on histology, appearance of cavitation, positive pleural fluid culture, results of PSB and BAL culture, and follow-up. MEASUREMENT AND RESULTS: A total of 110 episodes of suspected VAP were studied; 94 definite diagnoses were made (47 VAP, 47 no VAP). Using a threshold 1% of infected cells, BAL-D discriminated well between patients with and those without VAP (sensitivity 93.6%, specificity 91.5%, area under the receiver-operating characteristic curve 0.953). The senior clinical judgment was correct in 71% cases. It was correct in 78% and 94% of cases after airway visualization and BAL-D findings, respectively. After BAL-D the positive and negative predictive values in diagnosing VAP were 90% and 98%, respectively. However, the therapeutic plan was correct in only 65% using clinical judgment (15 untreated patients, 3 ineffective treatment, 15 useless treatment), 66% using airway visualization (14 untreated VAP, 4 ineffective treatment, 14 useless treatment), and 88% using BAL-D results (1 untreated patients, 6 ineffective, 4 useless), according to definite diagnosis and final antibiotic susceptibility testings. CONCLUSIONS: A strategy based on bronchoscopy and BAL-D generally leads to a rapid and appropriate treatment of nosocomial pneumonia in ventilated patients.

**Equal Aspiration Rates in Gastrically and Transpylorically Fed Critically Ill Patients**—Esparza J, Boivin MA, Hartshorne MF, Levy H. Intensive Care Med 2001;27(4):660–664.

OBJECTIVES: To determine the difference in aspiration rates between gastrically and transpylorically fed patients in the intensive care unit. DESIGN: A prospective controlled study of critically ill patients randomized to receive either a gastrically placed feeding tube or a transpylorically placed feeding tube. SETTING: University teaching hospital's medical intensive care unit. The study was conducted over 14 months.

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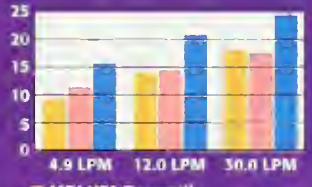


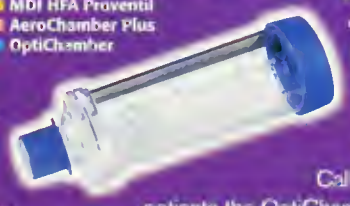

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1) Wojciechowski W. *Respir Care* 2001;47 (Abstract No. OF-21-122):1082.
2) Data accepted for presentation at the 2001 American College of Allergy, Asthma & Immunology Annual Meeting.
3) Asmus MJ, et al. *Am J Respir Crit Care Med* 2001;163 (5):A444.


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PATIENTS: Fifty-four critically ill subjects (with an overall 40% mortality) with similar baseline age, severity of illness, and nutritional needs requiring enteral nutrition, with 51 completing the study. INTERVENTIONS: All feeds were tagged with technetium-99m radiolabeled sulfur colloid, and the pulmonary secretions or lungs of each patient were scanned on a daily basis to determine whether aspiration had occurred. Patients were fed according to their assigned tube placement which was verified daily by continuous electromyography. MEASUREMENTS AND RESULTS: Of 27 gastrically fed patients 2 (7%) had evidence of scanned feed in pulmonary secretions or the lung, compared to 3 of 24 (13%) transpylorically fed patients (n.s.). Clinical suspicion of aspiration was insensitive and detected only 60% of isotopically documented aspirations with a positive predictive value of 27%. CONCLUSION: There was no difference in aspiration rates between gastrically and transpylorically fed critically ill patients.

**Acid-Base Alterations in Heatstroke**—Bouchama A, De Vol EB. Intensive Care Med 2001;27(4):680–685.

OBJECTIVE: To analyze the acid-base balance during heatstroke. DESIGN: Retrospective study. SETTING: Heatstroke Center, Makkah, Saudi Arabia. PATIENTS: Hundred nine consecutive heatstroke patients (mean age 55 ± 12 years) with rectal temperature from 40 to 43.4 °C following exposure to hot weather. INTERVENTION: Arterial blood gases collected prospectively and analyzed using 95% confidence limits established by controlled experimental studies. Severity of heatstroke on admission assessed by Simplified Acute Physiology Score and Organ System Failure score. RESULTS: Metabolic acidosis was the predominant acid-base change followed by respiratory alkalosis (81 and 55% of the patients, respectively). The prevalence of metabolic acidosis (but not respiratory alkalosis) was significantly associated with the degree of hyperthermia: 63, 95 and 100% at 41, 42 and 43 °C, respectively ($p < 0.0001$). Patients with metabolic acidosis had a large anion gap (24 ± 5). Arterial partial pressure of oxygen ($P_{aO_2}$), systolic blood pressure and Organ System Failure score were similar with or without metabolic acidosis. Although the acute physiology score was higher in patients with, than without, metabolic acidosis (15.7 ± 3.7 vs 9.8 ± 4.4, $p < 0.001$), there was no significant difference in neurologic morbidity and mortality (7.9 vs 1.1%, 5.6 vs 0%, $p = 0.776$ and 0.581, respectively). CONCLUSION: We conclude that metabolic acidosis is the predominant response in heatstroke.

**Clinical Features of Patients with Acute Organophosphate Poisoning Requiring Intensive Care**—Lee P, Tai DY. Intensive Care Med 2001; 27(4):694–699.

OBJECTIVES: To describe the clinical features of organophosphate poisoning (OPP), to evaluate the Acute Physiology and Chronic Health Evaluation (APACHE) II score as an alternative index for measuring OPP severity, and to assess cholinesterase levels for predicting successful weaning from mechanical ventilation (MV). DESIGN AND SETTING: Retrospective medical record review in a medical intensive care unit of an acute general hospital. PATIENTS: Twenty-three adults with OPP between 1995 and 1999. All cases were due to malathion poisoning. Muscarinic features were the predominant clinical manifestations (83%), followed by central nervous system (78%) and nicotinic manifestations (17%). RESULTS: MV was required by 74% of patients because of bronchial secretions (83%), altered conscious level (78%), pneumonia (78%), and flaccid paralysis (57%). Five patients (22%) had features of intermediate syndrome. ICU mortality was 13% and the mean ICU stay was 9.1 ± 6.0 days. The mean APACHE II score was 17.4 ± 7.4 and it correlated with mortality, severity of OPP, length of MV, and cholinesterase level. An APACHE II score of 26 or higher was predictive of mortality, with 95% sensitivity and 100% specificity. Threshold levels of serum and red blood cell cholinesterase for successful weaning from MV were 2,900 U/l and 7,500 U/l, respectively. CONCLUSIONS: The APACHE II score may be used as an alternative index of severity in patients with OPP; a score of 26 or higher is a good predictor of mortality. Cholinesterase levels are useful in predicting successful weaning of patients from MV.

**A Prospective Cohort Study of 6-Month Mortality in a Community Hospital Experiencing a Gradual Reduction in Critical Care Services**—Walther SM, Jonasson U. Intensive Care Med 2001;27(4):700–705.

OBJECTIVE: To analyse the effect of reduction of critical care services on admissions, resource consumption and outcome. DESIGN: Observation outcome study with analysis of patient data collected prospectively during 1993, 1995 and 1997. SETTING: High dependency and intensive care unit (HDU/ICU) of a community hospital serving a population of 168,000. The number of beds decreased from 12 (1993), to 10 (1995) and to 8 (1997) with concomitant decrease in staff. PATIENTS AND PARTICIPANTS: Three patient cohorts admitted to the HDU/ICU during 1993, 1995 and 1997. MEASUREMENTS AND RESULTS: Admissions were classified into recovery room care or critical care admissions and stratified according to workload (Levels I-IV). Illness severity scores of critical care admissions were recorded according to the APACHE II system. Mortality data were acquired from a national database. The total number of admissions to the unit did not change over the years. Length of stay decreased significantly over the years. Standardised mortality rates based on mortality within 30 days of discharge from the HDU/ICU were 1.17 (95% confidence interval 0.96–1.43) for critical care admissions during 1993, 0.86 (0.70–1.06) for 1995 and 0.98 (0.79–1.22) for 1997. Survival 180 days after discharge from the HDU/ICU did not differ significantly over the years. CONCLUSIONS: The results suggest that an excess of resources were used in critical care services during 1993 and 1995. Reduction of HDU/ICU beds by 30% from 7.1 to 4.8 beds/100,000 was not associated with increased 6-month mortality of the patients admitted.

**How Safe Is Non-Bronchoscopic Bronchoalveolar Lavage in Critically Ill Mechanically Ventilated Children?**—Burmester M, Mok Q. Intensive Care Med 2001;27(4):716–721.

OBJECTIVE: To assess the safety of non-bronchoscopic bronchoalveolar lavage (NB-BAL) in critically ill mechanically ventilated children. SETTING: Paediatric intensive care unit in a tertiary children's hospital. METHODS: The data from 60 consecutive critically ill mechanically ventilated children who underwent NB-BAL was reviewed from November 1997 to December 1999. PRISM score prior to NB-BAL, observations at the time of NB-BAL and arterial blood gases, oxygenation index (OI), ventilator settings, haemodynamic variables and temperature taken at 1 h before, and 1 and 6 h after NB-BAL, were retrieved from the archived computerised database. RESULTS: Median age was 7 months (IQR 2.8–43 months) and median weight was 5.5 kg (IQR 4–14 kg). Four (7%) patients exhibited significant immediate complications, requiring escalation of respiratory or haemodynamic support. Forty-two (70%) patients had complete data for calculation of OI; there was no significant change in median OI at 1 and 6 h after NB-BAL. However 5 (12%) of these patients experienced an increase in OI of between 10 and 45 at 1 h post NB-BAL, which returned to baseline at 6 h post NB-BAL. Complications did not correlate with any of the available variables: baseline OI, PRISM score or with deterioration at the time of the procedure, although it was observed that four out of the six patients with baseline OIs of greater than 20 experienced complications. CONCLUSION: Non-bronchoscopic bronchoalveolar lavage in critically ill mechanically ventilated neonates and children is generally a well-tolerated procedure, but for some patients, in whom it was not possible to elucidate predictive factors, complications developed. All patients, particularly those with

OIs of greater than 20, require careful monitoring during and after the procedure.

**Outcome of Long-Stay Intensive Care Patients**—Hughes M, MacKirdy FN, Norrie J, Grant IS. Intensive Care Med 2001;27(4):779–782.

OBJECTIVES: To assess the numbers, characteristics and outcome for patients requiring long-term intensive care. DESIGN AND SETTING: Observational cohort study in 23 Scottish intensive care units over a 3-year period. PATIENTS AND PARTICIPANTS: 323 patients with an ICU stay of 30 days or more. MEASUREMENTS AND RESULTS: Although representing only 1.6% of patients, those with long stays occupied 15.7% of bed-days. Hospital survival among these patients was 59.9%. With the available data it was not possible to discriminate survivors from non-survivors. CONCLUSIONS: Since these patients have a relatively high hospital survival, resources should not be withheld from them on the basis of prolonged ICU stay alone, even in countries with limited ICU provision.

**Monitoring End-Tidal Carbon Dioxide During Weaning from Cardiopulmonary Bypass in Patients Without Significant Lung Disease**—Maslow A, Stearns G, Bert A, Feng W, Price D, Schwartz C, et al. Anesth Analg 2001;92(2):306–313.

End-tidal carbon dioxide tension ($P_{ETCO_2}$) changes with fluctuations in cardiac output (CO). We compared $P_{ETCO_2}$ to pulmonary artery blood flow (PAQt) during weaning from cardiopulmonary bypass (CPB) in normothermic patients without significant pulmonary disease. Fifteen consecutive adult cardiac surgical patients were prospectively studied during and shortly after weaning from CPB. Before separation from CPB, $P_{ETCO_2}$ and PAQt were measured, the latter by transesophageal Doppler echocardiography. At the time of measurements patients were normothermic, and ventilated at 6 breaths/min with tidal volumes of 10 mL/kg. After separation from CPB, thermodilution cardiac output (TDCO) was measured in addition to PAQt and $P_{ETCO_2}$. Regression and bias analyses were used to compare $P_{ETCO_2}$, PAQt, and TDCO. Seventy measurements were recorded; 31 before separation from CPB and 39 after separation from CPB. A good correlation was seen between PAQt and $P_{ETCO_2}$ ($r = 0.88$) and between TDCO and PAQt ($r = 0.93$; mean bias 0.03 L/min; SD 0.52 L/min). The regression analysis of PAQt on $P_{ETCO_2}$ showed greater variability at $P_{ETCO_2}$ levels > 34 mm Hg ($n = 22$; $r = 0.14$). Increases in $P_{ETCO_2}$ plateaued at this level, although PAQt continued to increase. When $P_{ETCO_2}$ was more than 30 mm Hg, all PAQt and TDCO values were >4.0 L/min (>2.0 L/min/m$^2$). When $P_{ETCO_2}$ exceeded 34 mm Hg, all values of PAQt, and 28/29 values of TDCO were more than 5 L/min (>2.5 L/min/m$^2$). One patient had TDCO of 4.69 L/min (2.39 L/min/m$^2$). In normothermic patients without significant pulmonary disease, $P_{ETCO_2}$ is a useful index of PAQt during separation from CPB. Under the clinical settings in this study, a $P_{ETCO_2}$ greater than 30 mm Hg was invariably associated with a CO more than 4.0 L/min or a cardiac index >2.0 L/min/m$^2$.

**The Efficacy of Esophageal Detector Devices in Verifying Tracheal Tube Placement: A Randomized Cross-Over Study of Out-of-Hospital Cardiac Arrest Patients**—Tanigawa K, Takeda T, Goto E, Tanaka K. Anesth Analg 2001;92(2):375–378.

We performed this prospective study to evaluate the efficacy of esophageal detector devices (EDDs), both the bulb and the syringe-type, to indicate positioning of endotracheal tubes (ETTs) in out-of-hospital cardiac arrest patients. Forty-eight adult patients with out-of-hospital cardiac arrest were enrolled. Immediately after tracheal intubation and ETT cuff inflation in the emergency department, the patients were allocated randomly to two cross-over groups. In Group 1 ($n = 24$), patients underwent a bulb test and a syringe test in sequence. In Group 2 ($n = 24$), patients


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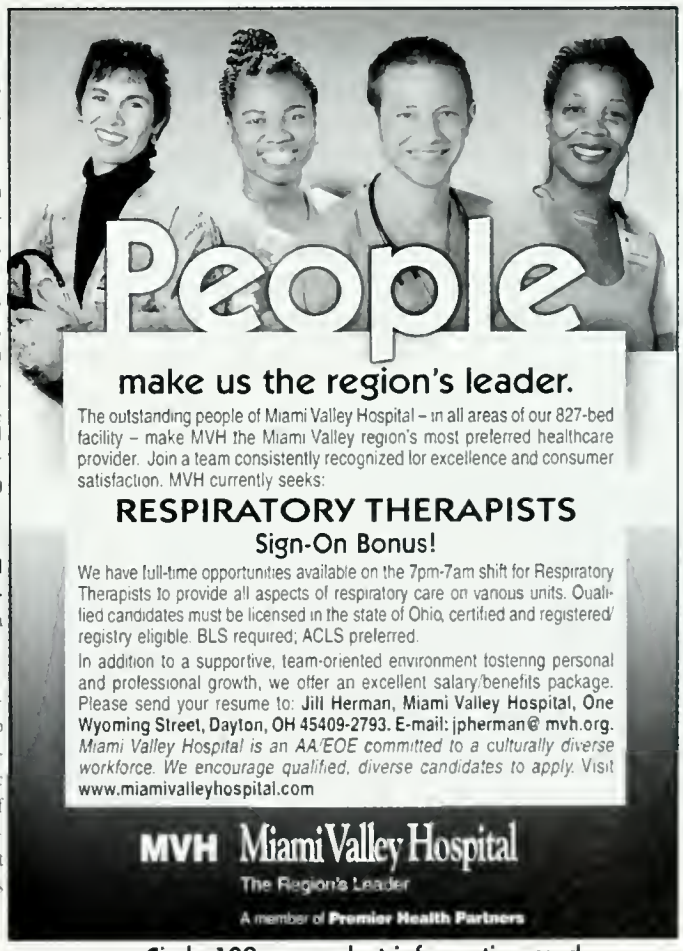
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underwent a syringe test and a bulb test in sequence. End-tidal carbon dioxide ($ETCO_2$) was also monitored. In 56 attempts at tracheal intubation, the bulb, the syringe, and $ETCO_2$ indicated all eight esophageal intubations. In 48 tracheal intubations, the bulb test correctly indicated 34 tracheal intubations (sensitivity, 70.8%). The syringe test identified 35 tracheal intubations (sensitivity, 72.9%). The results of both tests agreed in 33 tracheal intubations. $ETCO_2$ was detected in 31 tracheal intubations (sensitivity, 64.6%). No statistical difference was found among the tests. EDDs were less sensitive in detecting tracheal intubation for out-of-hospital cardiac arrest patients. Therefore, proper clinical judgment in conjunction with these devices should be used to confirm ETT placement in these difficult situations.

**The Effect of Continuous Positive airway Pressure on Cerebral Blood Flow Velocity in Awake Volunteers**—Bowie RA, O'Connor PJ, Hardman JG, Mahajan RP. Anesth Analg 2001;92(2):415–417.

We measured the effect of 5 and 10 cm $H_2O$ continuous positive airways pressure (CPAP) on middle cerebral artery blood flow velocity (FV) in 15 awake, healthy volunteers by using transcranial Doppler ultrasonography. Mean, systolic, and diastolic FV plus pulsatility index were recorded. No significant change in any measured variable was observed with the application of 5 or 10 cm $H_2O$ CPAP. These results are in contrast to those of a previous study, which found a significant increase in mean FV and a decrease in pulsatility index during the application of 12 cm $H_2O$ CPAP.

**Inspiratory Lung Impedance in COPD: Effects of PEEP and Immediate Impact of Lung Volume Reduction Surgery**—Kaczka DW, Ingenito EP, Body SC, Duffy SE, Mentzer SJ, DeCamp MM, Lutchen KR. J Appl Physiol 2001;90(5):1833–1841.

Frequency-dependent characteristics of lung resistance (RL) and elastance (EL) are sensitive to different patterns of airway obstruction. We used an enhanced ventilator waveform (EVW) to measure inspiratory RL and EL spectra in ventilated patients during thoracic surgery. The EVW delivers an inspiratory flow waveform with enhanced spectral excitation from 0.156 to 8.1 Hz. Estimates of the coefficients in a trigonometric approximation of the EVW flow and transpulmonary pressure inspirations yielded inspiratory RL and EL spectra. We applied the EVW in a group with mild obstruction undergoing various thoracoscopic procedures (n = 6), and another group with severe chronic obstructive pulmonary disease undergoing lung volume reduction surgery (n = 8). Measurements were made at positive end-expiratory pressure (PEEP) of 0, 3, and 6 $cmH_2O$. Inspiratory RL was similar in both groups despite marked differences in spirometry. The chronic obstructive pulmonary disease patients demonstrated a pronounced frequency-dependent increase in inspiratory EL consistent with severe heterogeneous peripheral airway obstruction. PEEP appears to have beneficial effects by reducing peripheral airway resistance. Lung volume reduction surgery resulted in increased inspiratory RL and EL at all frequencies and PEEPs, possibly due to loss of diseased lung tissue, pulmonary edema, increased mechanical heterogeneity, and/or an improvement in airway tethering.

**Assessment of Respiratory System Mechanics by Artificial Neural Networks: An Exploratory Study**—Perchiazzi G, Hogman M, Rylander C, Giuliani R, Fiore T, Hedenstierna G. J Appl Physiol 2001;90(5):1817–1824.

We evaluated 1) the performance of an artificial neural network (ANN)-based technology in assessing the respiratory system resistance (Rrs) and compliance (Crs) in a porcine model of acute lung injury and 2) the possibility of using, for ANN training, signals coming from an electrical analog (EA) of the lung. Two differently experienced ANNs were compared. One ANN ($ANN_{BIO}$) was trained on tracings recorded at different time points after the administration of oleic acid in 10 anesthetized and paralyzed pigs during constant-flow mechanical ventilation. A second ANN ($ANN_{MOD}$) was trained on EA simulations. Both ANNs were evaluated prospectively on data coming from four different pigs. Linear regression between ANN output and manually computed mechanics showed a regression coefficient (R) of 0.98 for both ANNs in assessing Crs. On Rrs, $ANN_{BIO}$ showed a performance expressed by R = 0.40 and $ANN_{MOD}$ by R = 0.61. These results suggest that ANNs can learn to assess the respiratory system mechanics during mechanical ventilation but that the assessment of resistance and compliance by ANNs may require different approaches.

**Effect of Manually Assisted Cough and Mechanical Insufflation on Cough Flow of Normal Subjects, Patients with Chronic Obstructive Pulmonary Disease (COPD), and Patients with Respiratory Muscle Weakness**—Sivasothy P, Brown L, Smith IE, Shneerson JM. Thorax 2001;56(6):438–444.

BACKGROUND: It has been suggested that cough effectiveness can be improved by assisted techniques. The effects of manually assisted cough and mechanical insufflation on cough flow physiology are reported in this study. METHODS: The physiological actions and patient self-assessment of manually assisted cough and mechanical insufflation were investigated in 29 subjects (nine normal subjects, eight patients with chronic obstructive pulmonary disease (COPD), four subjects with respiratory muscle weakness (RMW) with scoliosis, and eight subjects with RMW without scoliosis). RESULTS: The peak cough expiratory flow rate and cough expiratory volume were not improved by manually assisted cough and mechanical insufflation alone or in combination in normal subjects. The median increase in peak cough expiratory flow in subjects with RMW without scoliosis with manually assisted cough alone or in combination with mechanical insufflation of 84 L/min (95% confidence interval (CI) 19 to 122) and 144 L/min (95% CI 14 to 195), respectively, reflects improvement in the expulsive phase of coughing by these techniques. Manually assisted cough and mechanical insufflation in combination raised peak expiratory flow rate more than either technique alone in this group. The abnormal chest shape in scoliotic subjects and the fixed inspiratory pressure used made effective manually assisted cough and mechanical insufflation difficult in this group and no improvements were found. In patients with COPD manually assisted cough alone and in combination with mechanical insufflation decreased peak expiratory flow rate by 144 L/min (95% CI 25 to 259) and 135 L/min (95% CI 30 to 312), respectively. CONCLUSIONS: Manually assisted cough and mechanical insufflation should be considered to assist expectoration of secretions in patients with RMW without scoliosis but not in those with scoliosis.

**Method for Manipulating Peak Flow Measurements Producing Falsely Raised Readings**—Ross S, Cochran DP. Thorax 2001;56(6):500–501.

Methods by which patients can artificially produce raised peak flow measurements have been described. We recently observed a patient manipulating the peak flow meter in a way that had not been described before. A study was therefore undertaken to determine if this technique could repeatedly produce clinically significant changes in peak flow readings. Fifteen adults, using a mini-Wright peak flow meter, made five measurements using the correct technique followed by five manipulated measurements under observation. Significant increases in peak flow measurements were observed in 14 of the 15 subjects. The mean increase in peak flow rate using the incorrect technique was 56% (range -4% to 86%). Clinicians should be aware that patients might employ this technique to manipulate measurements which could have consequences for management.

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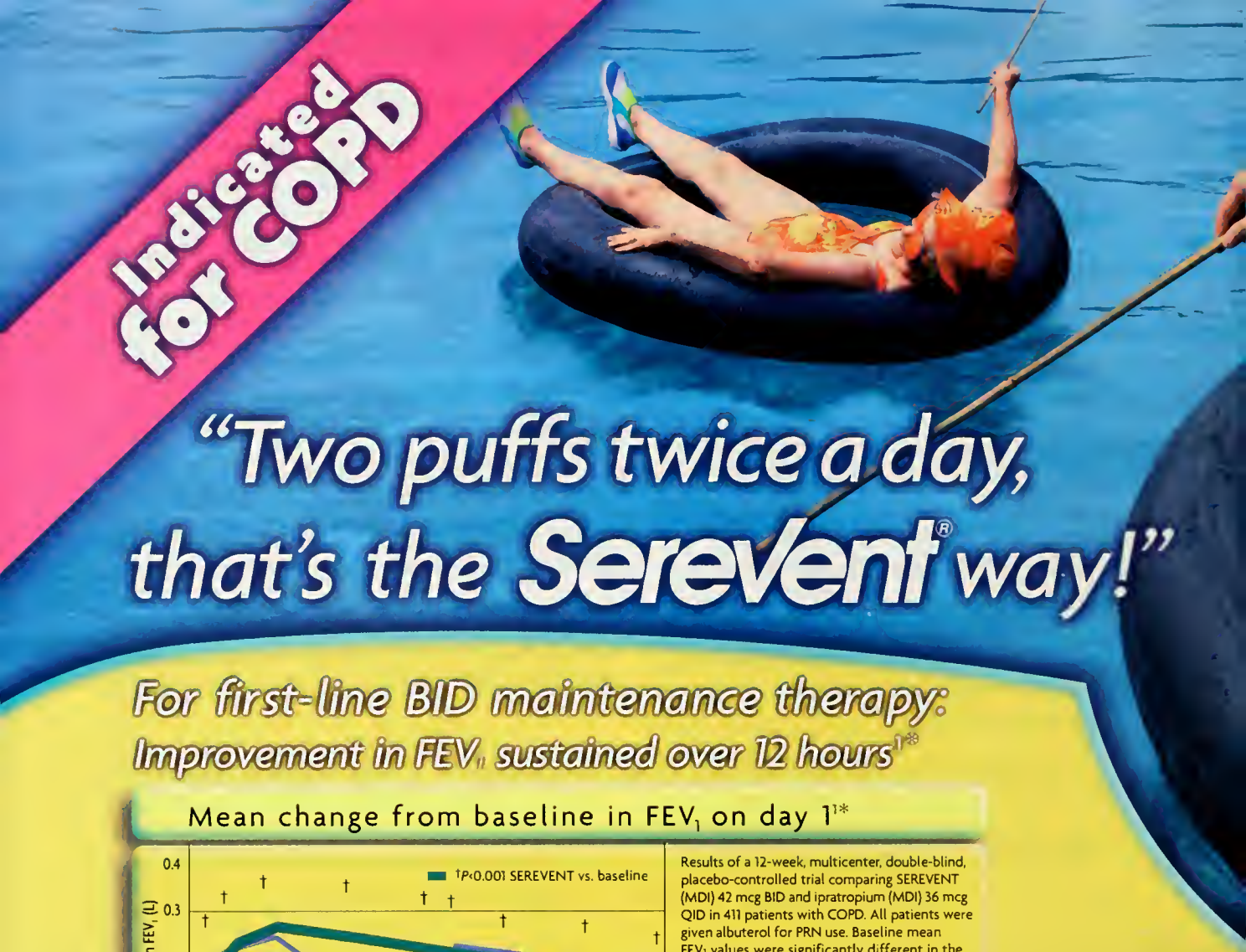


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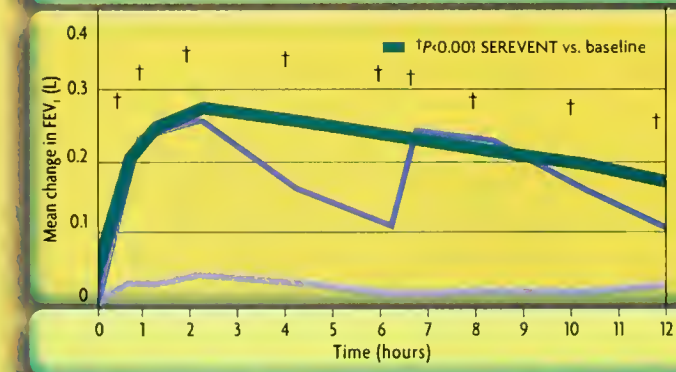


Results of a 12-week, multicenter, double-blind, placebo-controlled trial comparing SEREVENT (MDI) 42 mcg BID and ipratropium (MDI) 36 mcg QID in 411 patients with COPD. All patients were given albuterol for PRN use. Baseline mean $FEV_1$ values were significantly different in the ipratropium group vs. the placebo and SEREVENT groups ($P \leq 0.01B$).

- SEREVENT (n=131) Baseline=1.28 L
- Ipratropium (n=129) Baseline=1.16 L
- Placebo (n=136) Baseline=1.30 L

*Adapted from Mahler et al.*[1]

*In clinical trials, no statistically significant difference in $FEV_1$ was seen between SEREVENT and ipratropium.

- *Daytime use of rescue albuterol reduced by 57% versus baseline at 12 weeks (baseline rescue albuterol 4.6 puffs/day)*[1]
- *Sustained efficacy over a 12-week period*[1]
- *In clinical trials, no consistently significant differences were seen among the treatment groups in the following parameters: 6-minute walk, quality-of-life symptom scores, dyspnea, incidence of exacerbations*

When beginning treatment with SEREVENT Inhalation Aerosol, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute COPD symptoms (see PRECAUTIONS: Information for Patients in complete Prescribing Information).

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO RELIEVE ACUTE COPD SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting, $beta_2$-agonist (e.g., albuterol) for treatment of acute COPD symptoms that occur despite regular twice-daily (morning and evening, approximately 12 hours apart) use of SEREVENT Inhalation Aerosol.

*Please see brief summary of Prescribing Information and reference on following pages.*

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BRIEF SUMMARY

## (salmeterol xinafoate) Inhalation Aerosol

**Bronchodilator Aerosol**
**For Oral Inhalation Only**

The following is a brief summary only; see full prescribing information for complete product information

**CONTRAINDICATIONS:** SEREVENT Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to salmeterol or any of its components

**WARNINGS:**

**IMPORTANT INFORMATION: SEREVENT INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, when SEREVENT Inhalation Aerosol has been initiated in this situation.**

**Although it is not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT Inhalation Aerosol in this setting is inappropriate.**

**SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting $beta_2$-agonist for this purpose as well as warn them that increasing inhaled $beta_2$-agonist use is a signal of deteriorating asthma.**

**SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when SEREVENT Inhalation Aerosol is initiated.**

**(See PRECAUTIONS: Information for Patients and the accompanying PATIENT'S INSTRUCTIONS FOR USE.)**

1. Do Not Introduce SEREVENT Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma: SEREVENT Inhalation Aerosol is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE section of full prescribing information) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT Inhalation Aerosol provides greater efficacy than or additional efficacy to inhaled, short-acting $beta_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, in patients receiving SEREVENT Inhalation Aerosol. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting $beta_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma

2. Do Not Use SEREVENT Inhalation Aerosol to Treat Acute Symptoms: An inhaled, short-acting $beta_2$-agonist, not SEREVENT Inhalation Aerosol, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT Inhalation Aerosol, the physician must also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT Inhalation Aerosol.

When beginning treatment with SEREVENT Inhalation Aerosol, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Inhaled, Short-Acting $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting $beta_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting $beta_2$-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting $beta_2$-agonist is used in an 8-week period in conjunction with SEREVENT Inhalation Aerosol, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT Inhalation Aerosol in this situation is not appropriate. SEREVENT Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of 2 inhalations.**

4. Do Not Use SEREVENT Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids. The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. There are no data demonstrating that SEREVENT Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating SEREVENT Inhalation Aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage. As with other inhaled $beta_2$-adrenergic drugs, SEREVENT Inhalation Aerosol should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the $QT_c$ interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm: SEREVENT Inhalation Aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, SEREVENT Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of SEREVENT Inhalation Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving SEREVENT Inhalation Aerosol.

SEREVENT Inhalation Aerosol, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SEREVENT Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the $QT_c$ interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, SEREVENT Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**PRECAUTIONS:**

**General:** 1. Use with Spacer or Other Devices: The safety and effectiveness of SEREVENT Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. No effects on glucose have been seen with SEREVENT Inhalation Aerosol at recommended doses. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT Inhalation Aerosol at recommended doses.

**Information for Patients:** See illustrated PATIENT'S INSTRUCTIONS FOR USE. **SHAKE WELL BEFORE USING.**

It is important that patients understand how to use SEREVENT Inhalation Aerosol appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

1. Shake well before using.
2. The action of SEREVENT Inhalation Aerosol may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded.
3. SEREVENT Inhalation Aerosol is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
4. Patients should not stop SEREVENT therapy for COPD without physician/provider guidance since symptoms may recur after discontinuation.
5. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.
   - Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
   - Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
   - Use of 4 or more inhalations per day of a short-acting $beta_2$-agonist for 2 or more days consecutively
   - Use of more than one 200-inhalation canister of an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) in an 8-week period
6. SEREVENT Inhalation Aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT Inhalation Aerosol.
7. Patients should be cautioned regarding common adverse cardiovascular effects, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
8. In patients receiving SEREVENT Inhalation Aerosol, other inhaled medications should be used only as directed by the physician.
9. When using SEREVENT Inhalation Aerosol to prevent exercise-induced bronchospasm, patients should take the dose at least 30 to 60 minutes before exercise.
10. If you are pregnant or nursing, contact your physician about use of SEREVENT Inhalation Aerosol.
11. Effective and safe use of SEREVENT Inhalation Aerosol includes an understanding of the way that it should be administered.

**Drug Interactions:** ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical asthma trials (n=184), the mean daily need for additional $beta_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least 8 inhalations per day at least on 1 occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over 4 inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than 8 inhalations per day of short-acting $beta_2$-agonists with SEREVENT Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving SEREVENT Inhalation Aerosol, nebulized albuterol (1 dose in most) led to improvement in $FEV_1$ and no increase in occurrence of cardiovascular adverse events.

***Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:*** Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

***Corticosteroids and Cromoglycate:*** In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of SEREVENT Inhalation Aerosol when administered concurrently.

***Methylxanthines:*** The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving SEREVENT Inhalation Aerosol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by SEREVENT Inhalation Aerosol therapy.

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as SEREVENT Inhalation Aerosol, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above (approximately 9 times the maximum recommended daily inhalation dose in adults based on comparison of the areas under the plasma concentration versus time curves [AUCs]) caused dose-related increases in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (comparable to the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

In a 24-month inhalation and oral carcinogenicity study in Sprague Dawley rats, salmeterol caused dose-related increases in the incidence of mesovarian leiomyomas and ovarian cysts at inhalation and oral doses of 0.68 mg/kg per day and above (approximately 55 times the maximum recommended human daily inhalation dose in adults on a $mg/m^2$ basis). No tumors were seen at 0.21 mg/kg per day (approximately 15 times the maximum recommended human daily inhalation dose in adults on a $mg/m^2$ basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a $mg/m^2$ basis).

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a mg/m$^2$ basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose in adults based on the comparison of the AUCs), salmeterol xinafoate exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at oral doses of 10 mg/kg (approximately 1600 times the maximum recommended human daily inhalation dose on a mg/m$^2$ basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with SEREVENT Inhalation Aerosol in pregnant women. SEREVENT Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Use in Labor and Delivery:** There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SEREVENT Inhalation Aerosol for prevention of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

**Nursing Mothers:** Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in milk. However, since there is no experience with use of SEREVENT Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

**Pediatric Use:** The safety and effectiveness of SEREVENT Inhalation Aerosol in children younger than 12 years of age have not been established.

**Geriatric Use:** Of the total number of patients who received SEREVENT Inhalation Aerosol in all asthma clinical studies, 241 were 65 years of age and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in 4 well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in 2 large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the 2 latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

In 2 large, randomized, double-blind, placebo-controlled 3-month studies involving patients with COPD, 133 patients using SEREVENT Inhalation Aerosol were 65 years and older. These patients experienced similar improvements in FEV$_1$ as observed for patients younger than 65.

No apparent differences in the efficacy and safety of SEREVENT Inhalation Aerosol were observed when geriatric patients were compared with younger patients in asthma and COPD clinical trials. As with other beta$_2$-agonists, however, special caution should be observed when using SEREVENT Inhalation Aerosol in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

**ADVERSE REACTIONS:** Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia; palpitations, immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache, tremor; nervousness, and paradoxical bronchospasm (see WARNINGS).

**Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients 12 years of age and older with asthma. Table 1 reports the incidence of adverse events in these 2 studies.

**Table 1: Adverse Experience Incidence in 2 Large 12-Week Asthma Clinical Trials***

| | Percent of Patients | | |
|---|---|---|---|
| Adverse Event Type | Placebo n=187 | SEREVENT Inhalation Aerosol 42 mcg twice daily n=184 | Albuterol Inhalation Aerosol 180 mcg 4 times daily n=185 |
| Ear, nose, and throat | | | |
| Upper respiratory tract infection | 13 | 14 | 16* |
| Nasopharyngitis | 12 | 14 | 11 |
| Disease of nasal cavity/sinus | 4 | 6 | 1 |
| Sinus headache | 2 | 4 | <1 |
| Gastrointestinal | | | |
| Stomachache | 0 | 4 | 0 |
| Neurological | | | |
| Headache | 23 | 28 | 27 |
| Tremor | 2 | 4 | 3 |
| Respiratory | | | |
| Cough | 6 | 7 | 3 |
| Lower respiratory infection | 2 | 4 | 2 |

*The only adverse experience classified as serious was 1 case of upper respiratory tract infection in a patient treated with albuterol.

Table 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

***Cardiovascular:*** Tachycardia, palpitations.

***Ear, Nose, and Throat:*** Rhinitis, laryngitis.

***Gastrointestinal:*** Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.

***Hypersensitivity:*** Urticaria.

***Mouth and Teeth:*** Dental pain.

***Musculoskeletal:*** Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.

***Neurological:*** Nervousness, malaise/fatigue.

***Respiratory:*** Tracheitis/bronchitis.

***Skin:*** Rash/skin eruption.

***Urogenital:*** Dysmenorrhea.

Data from small dose-response studies show an apparent dose relationship for tremor, nervousness, and palpitations.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or might otherwise be expected with the use of inhaled corticosteroids.

**COPD:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients with COPD. Table 2 reports the incidence of adverse events in these 2 studies.

**Table 2: Adverse Experience Incidence in 2 Large 12-Week COPD Clinical Trials**

| | Percent of Patients | | |
|---|---|---|---|
| Adverse Event Type | Placebo n=278 | SEREVENT Inhalation Aerosol 42 mcg twice daily n=267 | Ipratropium Inhalation Aerosol 36 mcg 4 times daily n=271 |
| Ear, nose, and throat | | | |
| Upper respiratory tract infection | 7 | 9 | 9 |
| Sore throat | 3 | 8 | 6 |
| Nasal sinus infection | 1 | 4 | 2 |
| Gastrointestinal | | | |
| Diarrhea | 3 | 5 | 4 |
| Musculoskeletal | | | |
| Back pain | 3 | 4 | 3 |
| Neurological | | | |
| Headache | 10 | 12 | 8 |
| Respiratory | | | |
| Chest congestion | 3 | 4 | 3 |

Table 2 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Common cold, rhinorrhea, bronchitis, cough, exacerbation of chest congestion, chest pain, and dizziness occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

***Ear, Nose, and Throat:*** Cold symptoms, earache, epistaxis, nasal congestion, nasal sinus congestion, sneezing.

***Gastrointestinal:*** Nausea, dyspepsia, gastric pain, gastric upset, abdominal pain, constipation, heartburn, oral candidiasis, xerostomia, vomiting, surgical removal of tooth.

***Musculoskeletal:*** Leg cramps, myalgia, neck pain, pain in arm, shoulder pain, muscle injury of neck.

***Neurological:*** Insomnia, sinus headache.

***Non-Site Specific:*** Fatigue, fever, pain in body, discomfort in chest.

***Respiratory:*** Acute bronchitis, dyspnea, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, shortness of breath, wheezing.

***Urogenital:*** Urinary tract infection.

***Electrocardiographic Monitoring in Patients With COPD:*** Continuous electrocardiographic (Holter) monitoring was performed on 284 patients in 2 large COPD clinical trials during five 24-hour periods. No cases of sustained ventricular tachycardia were observed. At baseline, non-sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3 (3.0%) patients in the placebo, SEREVENT, and ipratropium groups, respectively. During treatment, nonsustained, asymptomatic ventricular tachycardia that represented a clinically significant change from baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo, SEREVENT, and ipratropium, respectively. Four of these cases of ventricular tachycardia were reported as adverse events (1 placebo, 3 SEREVENT) by 1 investigator based upon review of Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain (ipratropium) and reported as an adverse event.

**Observed During Clinical Practice:** In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

The following events have also been identified during postapproval use of SEREVENT in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to SEREVENT.

***Respiratory:*** Rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

***Cardiovascular:*** Hypertension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles).

**OVERDOSAGE:** The expected signs and symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the $QT_c$ interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of SEREVENT Inhalation Aerosol.

Treatment consists of discontinuation of SEREVENT Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of SEREVENT Inhalation Aerosol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in rats at inhalation doses of 2.9 mg/kg (approximately 240 times the maximum recommended human daily inhalation dose on a mg/m$^2$ basis) and in dogs at 0.7 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m$^2$ basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6100 times the maximum recommended human daily inhalation dose on a mg/m$^2$ basis) and in rats at 1000 mg/kg (approximately 81,000 times the maximum recommended human daily inhalation dose on a mg/m$^2$ basis).


GlaxoWellcome

Glaxo Wellcome Inc.
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US Patent Nos. 4,992,474, 5,225,445, and 5,380,922

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**Reference: 1.** Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;115:957-965.



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Printed in USA SE2192R0 July 2001

Part I of Two Special Issues

# Evidence-Based Medicine in Respiratory Care

Containing the papers and discussions from a Journal Conference presented under the auspices of the American Respiratory Care Foundation.

Supported by unrestricted educational grants from GlaxoSmithKline and Salter Labs.

Conference faculty members—front row, from left: Neil R MacIntyre MD FAARC, Dean R Hess PhD RRT FAARC, Maureen O Meade MD MSc, Shelley C Mishoe PhD RRT FAARC, Gordon H Guyatt MD MSc, Brian H Rowe MD MSc. Back row, from left: Gordon D Rubenfeld MD MSc, Robert L Chatburn RRT FAARC, A Gray Ellrodt MD, Charles G Durbin Jr MD FAARC, W Ward Flemons MD, Mark R Tonelli MD MA. Not pictured: William J Sibbald MD

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# Foreword

## Evidence-Based Medicine in Respiratory Care

Respiratory care, like all health-related disciplines, has been part of the information explosion that has occurred over the past 25 years. The explosion of medical information and its increased accessibility have assisted the development of evidence-based medicine (EBM). EBM is the judicious identification, evaluation, and application of the most relevant information to make medical decisions. It provides a framework to understand and use the available evidence to inform clinical decisions.

Accessing and using information are key components of EBM. There are numerous resources to search for sources of evidence. In addition, a variety of strategies can be used to locate, use, and evaluate medical information. Resources available to search for evidence to inform clinical decisions include: (1) EBM databases, including the Cochrane Database of Systematic Reviews, (2) MEDLINE (Pub Med), (3) EMBASE/Excerpta Medica, and (4) subject specialist databases such as HealthSTAR.

The Cochrane Databases of Systematic Reviews and other EBM databases provide guidance for respiratory therapists and other health professionals to evaluate the level of evidence and its quality. The research in EBM is the methodical collection of studies that meet strict quality criteria. All or portions of these studies can then be merged, distilled, and interpreted (meta-analysis). The "discoveries" in EBM are systematic reviews developed from this evaluation of the effect and effectiveness of health care to increase the generalizability of findings. EBM research requires rigorous evaluation of scientific data to support approaches to health care. Several articles in this and in the December issue of RESPIRATORY CARE provide information on how EBM can be used to inform clinical decision-making in everyday practice. Other articles examine the various forms of evidence relevant to respiratory care in asthma, chronic obstructive pulmonary disease, sleep apnea, acute respiratory distress syndrome, pneumonia, airway secretions management, artificial airway management, and weaning from mechanical ventilation.

The Cochrane Collaboration is an international research initiative established to produce, maintain, and disseminate reviews of evidence. The Cochrane Collaboration was launched in 1993 to provide evidence needed for health care decision-making. The need for the Cochrane Collaboration (http://www.cochrane.org) arose from the following shortcomings of the traditional approach to identifying research data to guide clinical decisions:

- No decision-maker can stay abreast of the scientific literature.
- Editorials and reviews often do not specify the searching strategies used.
- Textbooks quickly become out of date, especially with regard to treatment recommendations.
- An expert searcher can find only about half of the randomized trials in MEDLINE.
- MEDLINE and EMBASE/Excerpta Medica cover only about half of the world's medical journals.
- Even when the results of trials can be located, they may be of low quality because of inadequate power or biases toward reporting positive results.
- Even high quality, systematic reviews can quickly become outdated.

In addition to the Cochrane Database of Systematic Reviews, other sources of EBM reviews include Clinical Evidence, ACP Journal Club, and the Database of Abstracts of Reviews of Effectiveness (DARE). These sources provide many EBM reviews of topics germane to respiratory care. For example, one of the review groups in the Cochrane Collaboration is the "Airways Group." Abstracts from these databases are generally available online free of charge, and full text articles are available by subscription through search engines such as OVID (available in many hospital libraries).

There are numerous forms of evidence in addition to EBM reviews that can inform clinical decision-making. In fact, the growth of EBM has heightened the awareness of the many complexities of using research data to make clinical decisions for the health care of individuals. There are many varied examples in the literature of what constitutes evidence. Different forms of evidence are derived from randomized controlled trials, case-controlled studies, cohort studies, systematic reviews, surveys, qualitative studies, and professional consensus. This and the following issue of RESPIRATORY CARE are intended to assist clinicians to efficiently retrieve the best evidence and to critically evaluate evidence for incorporation into their practice.

The conference reports presented herein summarize the current status of EBM and serve as a starting point for further investigation and application. The authors are internationally recognized authorities in EBM and respiratory care. We anticipate that these reports will inform the respiratory care community of the importance of EBM and increase awareness of EBM's applications and limitations in respiratory care practice. It is our hope that these reports will provide a valuable resource and stimulate a broader dialog on the application of an evidenced-based approach to respiratory care.

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# What Is Evidence-Based Medicine and Why Should It Be Practiced?

Victor M Montori MD and Gordon H Guyatt MD MSc

What Is Evidence-Based Health Care?
An Explicit and Formal Problem-Solving Strategy
From Traditional Hierarchies to the Hierarchy of Evidence
A Value-Laden Process in the Context of Clinical Expertise
How Do Clinicians Practice Evidence-Based Medicine? Resources and Examples
Case Example
Formulating the Question
Evidence
The Appraisal
The Application
Scenario Resolution
Summary

**Responding to the limitations of traditional expert recommendations as a guide to clinical practice, evidence-based medicine has presented a paradigm shift in the way clinicians learn and practice medicine. The practice of evidence-based medicine requires careful examination of the evidence, using a set of formal rules applied in an explicit manner. The clinician then judiciously applies the evidence to decision-making, with an understanding of the patient context and values. Using examples pertinent to respiratory therapists, we discuss evidence-based decision-making as a clinical problem-solving strategy, its basis on a hierarchy of evidence, and the interplay of values, preferences, expertise, and circumstances that affect its application. We briefly describe some resources available to obtain evidence reports and to learn to critically appraise and apply them.** *Key words: evidence-based medicine, evidence, decision-making.* [Respir Care 2001;46(11):1201–1211]

## What Is Evidence-Based Health Care?

### An Explicit and Formal Problem-Solving Strategy

Clinicians are constantly confronted with clinical problems: what is the best way of weaning a patient from a ventilator, or of improving the quality of life of a patient with chronic obstructive pulmonary disease (COPD)? Historically, clinicians found solutions to these problems in manuals, textbooks, or in the oral and written traditions of the hospital. Learners would trust their most senior, apparently erudite, or charismatic colleagues for their ability to understand physiology and its derangements and to apply that knowledge to the problem at hand. With time and experience, one would hope to obtain this seniority, erudition, or charisma and continue to hand down these tra-

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A version of this paper was presented by Dr Guyatt during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20–22, 2001, Banff, Alberta, Canada.

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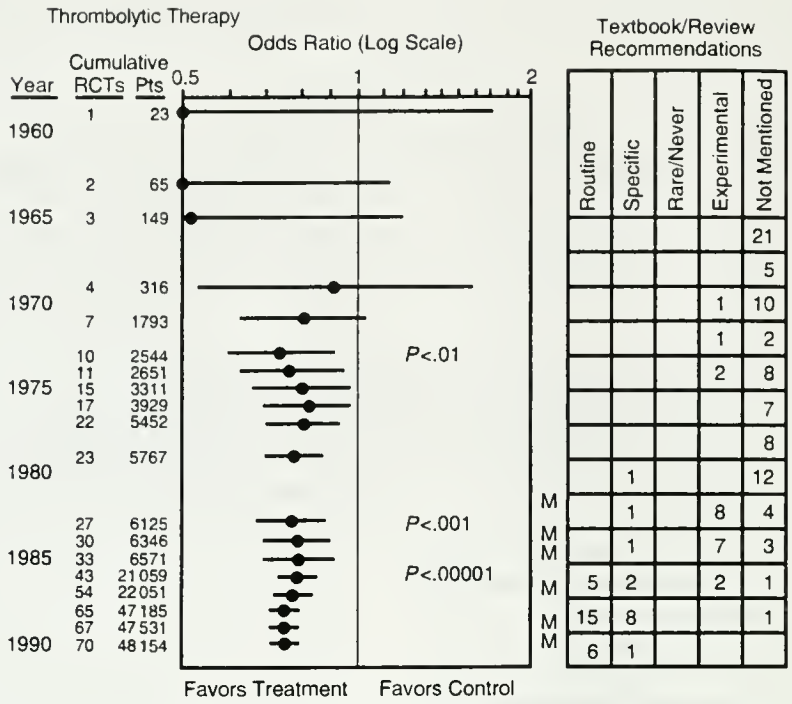


Fig. 1. Cumulative meta-analysis of the randomized trials that have investigated the impact of thrombolytic therapy on mortality after myocardial infarction. See text for explanation. RCT = randomized controlled trial. Pts = patients. (From Reference 1, with permission.)

ditions to junior colleagues, imparting with authority what was observed, learned, and practiced. That paradigm of education and practice resulted in wide variation in patterns of practice across institutions (or even across different authorities and their services within an institution) and patients would experience different outcomes, not all of them optimal.

At the same time, clinician-scientists conducted and published important clinical research. The results would potentially help decide on the best management strategies leading to the best patient outcomes. However, neither practitioners nor the authorities on whom they relied were equipped with the attitudes and skills to assess the value of those research findings or to judiciously incorporate that evidence into clinical practice. Thus, clinical research found suboptimal utilization.

The evolution of recommendations for therapy for patients suffering from myocardial infarction illustrates the limitations of traditional expert recommendations. The left side of Figure 1 presents a cumulative meta-analysis of the randomized trials that have investigated the impact of thrombolytic therapy on mortality after myocardial infarction.[1] The vertical line in the center of the figure represents an odds ratio of 1.0, the point at which there is no difference in mortality between treatment and control. Values to the left of that line represent a mortality reduction with treatment; values to the right represent an increase in mortality with treatment.

Investigators conducted the first randomized trial of thrombolytic therapy in the late 1950s, enrolling 23 patients and finding approximately half the number of deaths in treated patients as in control patients (thus, the point estimate of 0.5). With the very small sample size, the confidence interval (CI, represented by the horizontal lines associated with each point) was extremely wide. The second trial enrolled 42 patients, for a total of 65.

With the results of the tenth trial, and the randomization of over 2,500 patients, the CI no longer overlaps the line of no effect, suggesting that chance is becoming a less likely explanation of the apparent differences between treatment and control. By the mid-1980s, with over 6,500 patients enrolled, the CI was getting quite narrow, and the associated p value very small. Though there is some arbitrariness to the amount of evidence one requires before declaring treatment benefit definitively established, most would agree that the answer concerning thrombolytic therapy was in at that juncture.

This, however, did not stop investigators from randomizing more than 40,000 additional patients, of whom half did not receive thrombolysis. By 1990, with the random-

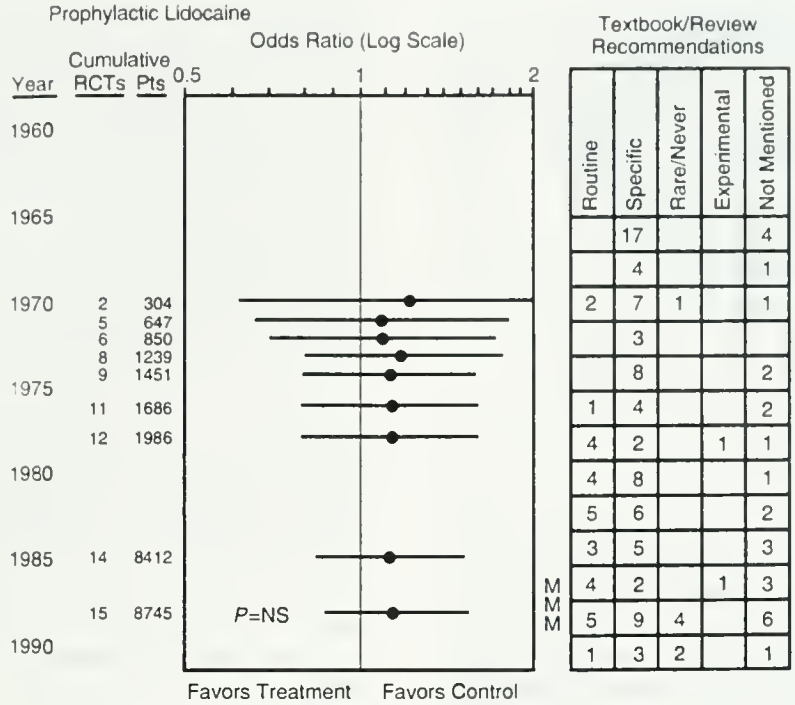


Fig. 2. Cumulative meta-analysis of the randomized trials that have investigated the impact of prophylactic lidocaine to prevent lethal ventricular arrhythmias in patients presenting with myocardial infarction. See text for explanation. M = meta-analysis. NS = not significant. (From Reference 1, with permission.)

ization of nearly 50,000 patients, the CIs around the odds ratio of approximately 0.75 (an odds reduction of 0.25) are very narrow indeed.

Why was it necessary to randomize so many additional patients after the data provided definitive support for the benefit of thrombolytic therapy? The right side of the figure provides at least part of the answer. That part of the figure, presenting the recommendations published by experts in textbooks and peer-reviewed journals as the evidence was accumulating, demonstrates considerable variability in expert opinion. In addition, there is considerable lag between the evidence and the expert recommendations. It was not until after 1990 that a consensus for administration of thrombolytic therapy developed.

This is far from the only example of this phenomenon. Figure 2 presents a similar cumulative meta-analysis, (and coincident expert recommendations) for prophylactic lidocaine to prevent lethal ventricular arrhythmias in patients presenting with myocardial infarction. Here the randomized trial evidence never supported therapy and in fact suggested a possible increase in mortality. Nevertheless, some experts continued to recommend prophylactic lidocaine until almost 1990. Clearly, the process by which experts reviewed the evidence and developed their treatment recommendations left something to be desired.

One sees the same sort of phenomenon in areas of practice more relevant to respiratory therapy. In a survey of intensive care units (ICUs) in Canada and France,[2] investigators found large practice variability in ventilator circuit and secretion management strategies. Of all ICUs, 97% and 61% ($p = 0.0004$) used the oral route for airway intubation in Canada and France, respectively. The ventilator circuit was changed with each new patient in 74% of ICUs in France and was changed in only 23% of ICUs in Canada ($p < 0.0001$). Other important differences included the use of heat and moisture exchangers and filters, use of closed endotracheal suction systems, and semirecumbent positioning. Those differences appeared to be explained by local culture, values, costs, and uncertainties about the evidence of efficacy for each intervention in preventing ventilator-associated pneumonia.

In the case of semirecumbent positioning, there have been 3 randomized studies showing decrease in aspiration in this body position[3–5] and 1 randomized trial showing its benefit in preventing ventilator-associated pneumonia.[6] ICUs need to nurse 4 mechanically ventilated patients (95% CI 3–11) in a semirecumbent position to prevent 1 clinically-diagnosed pneumonia. The survey of French and Canadian ICUs reported that 58% and 30% of patients, respectively, were nursed in the semirecumbent position. The directors of those ICUs cited nursing inconvenience and concern for adverse effects as the main reasons not to implement this low-cost strategy. As this example illustrates, under the traditional model, incorporation of evi-

dence into practice appears to be incomplete, variable from center to center, and lagging behind the research.

Ten years ago, evidence-based medicine was proposed as a shift from the traditional model to a new paradigm for problem solving that places a lower value on authority unsupported by empirical evidence.[7,8] Under this paradigm, decision-making requires careful examination of the evidence, using a set of formal rules applied in an explicit manner. Further, it requires the judicious application of research findings in the patient context, a sense of the availability of resources, and an understanding of the values of those involved in the clinical decision.

### From Traditional Hierarchies to the Hierarchy of Evidence

What constitutes evidence? By evidence we mean any empirical observation about the apparent relationship between events.[9] This means that the thoughtful observations of an experienced respiratory therapist constitute evidence, as do the observations derived from physiologic experiments and the results of large randomized clinical trials. Clinical observations differ from physiologic experiments and randomized trials in that the latter incorporate the purposeful introduction of safeguards against systematic error. The single practitioner will see a limited range of patients, and distortions that are an inevitable part of unsystematic human inference will affect the conclusions drawn from personal observations. These distortions are easily observed when we test a patient for a very rare condition we recently diagnosed in another patient, or when we remember the patient who benefited from an intervention that had no impact in a number of other patients we do not recall as vividly.[10]

Studies that measure physiologic variables in response to experimental manipulations are not subject to the same distortions, but might not accurately predict treatment effects on the outcomes that are important to patients, such as discomfort, disability, or death. For instance, physiologic rationale indicates that low oxygen saturation in arterial blood is a potent drive to breathe. COPD patients frequently develop exertional arterial oxygen desaturation and this contributes to dyspnea, the uncomfortable perception of labored breathing.[11] These observations led to the clinical hypothesis that oxygen supplementation, by decreasing the drive to breathe, would relieve exertional dyspnea in COPD patients. Investigators tested that hypothesis in a randomized trial of oxygen supplementation in the home in COPD patients with hypoxemia.[12] Patients and investigators were kept unaware of whether patients were receiving oxygen or air, and both physiologic and patient outcomes were measured. Patients suffered less arterial oxygen desaturation when receiving supplemental oxygen, but their exertional dyspnea and quality of life did not benefit from this intervention, compared to supplemental air.

Investigation of nitric oxide for decreasing mortality in critically ill ventilated patients with acute respiratory distress syndrome (ARDS) provides another example. Physiologic studies have shown that nitric oxide is a selective pulmonary vasodilator, improves ventilation/perfusion matching, and results in acute increases in arterial oxygen in many ARDS patients.[13] Unfortunately, 4 randomized trials[14–17] of nitric oxide in ARDS have resulted in relative risks of 0.9–1.2, and a pooled estimate of those trials suggests a trend toward harm (relative risk 1.12, 95% CI 0.9–1.4).

In a randomized trial, investigators allocate patients to treatment or control groups on the basis of chance, a process analogous to a coin flip. As sample size increases, randomization makes it increasingly likely that prognostic factors are balanced between treatment and control groups. In other words, in the absence of a treatment effect, outcomes in treatment and control groups will be more or less the same. Patients, caregivers, and those assessing outcome may all be blind to allocation in a randomized trial, further decreasing the likelihood of a biased estimate of treatment effect.

In an observational study, on the other hand, patients are allocated to treatment and control groups on the basis of their preference, their clinician's preference, or happenstance. Under those circumstances, the treatment and control groups usually have substantial imbalance of prognostic factors. Furthermore, blinding is not possible. As a result, estimates of treatment benefit based on observational studies focusing on outcomes that are important to patients are also dangerous. In many instances, observational studies appear to coincide with the results of randomized trials.[18,19] Nonetheless, it is impossible to know in an individual instance if the results of the observation study represent an accurate estimate, an underestimate, or more frequently, an overestimate of the true underlying treatment effect.

For example, in an observational study, oxygen supplementation during exercise was associated with improved exercise tolerance and dyspnea in COPD patients.[20] In contrast, the results of a randomized trial in COPD patients showed no difference in exercise tolerance or dyspnea between patients randomly allocated to receive oxygen or air during rehabilitation.[21]

Though the strength of inference (how sure we are of the causal relationship between an intervention or treatment and an outcome or end point) is greater for randomized trials than for observational studies, inference is further strengthened if results are consistent in a series of randomized controlled trials. For instance, a meta-analysis of 24 randomized trials of pulmonary rehabilitation in patients with severe COPD showed consistent and clinically

important improvements in measures of dyspnea and health-related quality of life, thus establishing the value of pulmonary rehabilitation in those patients.[22]

The same bias-minimizing strategies present in randomized controlled trials of many patients can be used to test treatments in individual patients.[23] In stable chronic conditions unlikely to resolve spontaneously, clinicians can conduct pairs of treatment periods in which a patient receives a different treatment in the 2 periods of each pair, with the order of periods within a pair determined by random allocation and with both patient and clinician blinded to the sequence. The trial continues until there is clear evidence that one of the treatments is better than the other. Clinicians have found such single-patient randomized (*n* of 1) trials useful in patients with asthma and COPD.[24,25] For instance, Patel et al completed 18 randomized *n* of 1 trials in COPD patients and found that 17 led to a definitive answer (ie, of the 2 strategies tested, one was clearly better than the other) and 8 led to discontinuation of an ineffective treatment. They also found that clinicians and patients participating in definitive trials were adhering to the superior strategy up to 40 months after completion of those trials.[26]

Evidence-based medicine proposes a hierarchy of evidence going from unsystematic clinical observations to *n* of 1 randomized trials (Table 1). Evidence from the top of the hierarchy should have greater impact in clinical decision-making than lower level observations. However, there are instances in which the benefit of treatment is so clear that evidence from a lower level in the hierarchy is enough to support clinical decisions: a randomized trial is not needed to determine if mechanically ventilating a somnolent patient with a partial pressure of carbon dioxide of 100 mm Hg yields a better outcome than continued medical management. Note that there is always evidence, even if it comes from the bottom of the hierarchy. The evidence may be extremely weak—such as the recollections of a more experienced colleague—but there is always evidence.

### A Value-Laden Process in the Context of Clinical Expertise

Knowledge of the best available evidence of treatment is not enough to recommend a particular course of action.

Table 1. Hierarchy of Evidence: Therapy or Prevention

| |
|---|
| *n* of 1 randomized trials |
| Meta-analyses of randomized trials |
| Randomized controlled trials |
| Systematic reviews of observational studies |
| Observational studies |
| Physiologic studies |
| Unsystematic clinical observations |

Fig. 3. The role of evidence in decision-making.

Patients present with different values, expectations, and preferences about their health care. We have met patients who would avoid prescription drugs in favor of "natural" approaches or who, because of their age or poor quality of life, would never accept intubation and mechanical ventilation. We have also met patients who, despite advanced age and severe functional impairment, wanted us to do everything possible to prolong their lives.

Among the preferences that clinicians must ascertain is the patient's desired level of involvement in decision-making. Some patients want to participate in the process of determining their optimal management, and, indeed, to make the final decisions about their care. At the other end of the spectrum are patients who do not want to discuss the alternatives and prefer to leave the final decisions to their caregivers. We could harm the first group of patients by not fully informing them or by not fully consulting them about our management decisions. We could harm the latter group by overwhelming them with information and asking them to make decisions. Health care practitioners must be mindful of the preferred decision-making style of the patient in the specific circumstances and be ready to adapt to changes of style along the way.[27]

Application of evidence must also account for the patient's particular circumstances. For instance, the patient with obstructive sleep apnea may not benefit from nasal continuous positive airway pressure if the patient will not adhere to therapy because her spouse cannot tolerate the machine's noise. The COPD patient offered domiciliary oxygen might not use it for fear of becoming dependent.[28]

In summary, evidence-based practice requires clinical expertise, common sense, understanding of the circumstances and values of the patient, and judicious application of the best available evidence (Figure 3).

## How Do Clinicians Practice Evidence-Based Medicine? Resources and Examples

### Case Example

Imagine you are an active member of the pulmonary rehabilitation team in the regional hospital. The new ad-

ministration is considering whether to expand the pulmonary rehabilitation program or to establish a geriatric day hospital in the same facility. To help make its case to the administration, your team decides to collect information about the efficacy of pulmonary rehabilitation.

### Formulating the Question

Health care practitioners are challenged to keep up with the explosion in medical research information. Recent progress in information technology (eg, the emergence of the Internet and the collection of literature in databases such as MEDLINE) has made it possible to search and retrieve information more efficiently (in terms of time and money) than ever before.

Evidence-based practice involves formulating focused questions pertinent to your practice, identifying the best available evidence to answer those questions, critically appraising the evidence to assess its validity or the likelihood of bias, and deciding whether the evidence applies to a specific situation.[29] The entire process hinges on the ability of the practitioner to correctly identify and describe the problem and to formulate a clear and focused question.[30]

A useful way to formulate clinical questions is to think of the patient, the interventions or exposures under comparison, and the outcome. For the rehabilitation team, the patients are those with COPD severe enough to result in marked functional limitation, the interventions are outpatient program versus usual community care, and the outcomes are the patients' quality of life and costs to the patient and the rest of society.

### Evidence

The next step is to search and retrieve the highest quality evidence available. Clinicians can seek evidence from a number of resources (Table 2). Practitioners frequently consult more expert colleagues who may be able to point to information in a very efficient and reassuring manner.[31] Often, those colleagues cannot describe the processes followed to search for and select the information they have. As a result, these processes cannot be scrutinized and may be open to bias. For instance, an expert colleague may remember reports discussed in a recent meeting, those highlighted in the high-impact journals, or those brought to his or her attention by equipment marketing representatives. Those sources could represent the newest, the most exciting, or the most impressive results and not the balanced and comprehensive picture needed to make important clinical decisions.

Just as your colleague's searching and selection processes are not amenable to appraisal, traditional review articles or book chapters suffer the same limitation. Often written by a single expert using no bias-limiting procedures to select and present the evidence, these reviews have historically lagged behind the best current evidence, sometimes contradicted that evidence, and frequently suffered from disagreement between authorities.[1,32] A recent

Table 2. Some Evidence Sources Available Today for the Practice of Evidence-Based Medicine

*Clinical Evidence*
- On-line: http://www.clinicalevidence.org
- Subscription: BMJ Publishing Group, OVID
- Focus: Primary care medicine
- Process: Explicit review process with attention to methodological quality
- Respiratory medicine topics represented: asthma, chronic obstructive pulmonary disease (COPD), community-acquired pneumonia, lung cancer, spontaneous pneumothorax, upper respiratory infections, bronchiolitis, thromboembolism.

*Best Evidence* (American College of Physicians [ACP] Journal Club, Evidence-based Medicine, Diagnostic Strategies for Common Medical Problems)
- On-line: http://www.acponline.org
- Subscription: American College of Physicians—American Society of Internal Medicine (CD-ROM), OVID
- Focus: Common medical problems in adult medicine
- Process: Explicit process of identifying studies (primary or reviews) by hand-searching journals for studies with sound methods and clinically relevant results. The studies are presented using structured abstracts followed by commentary from clinical experts.
- Respiratory medicine topics represented: Not limited by design.

*Cochrane Library*
- On-line: http://www.cochranelibrary.com
- Abstracts available on PubMed (see below)
- Subscription: Update Software, OVID (Evidence-based medicine reviews)
- Focus: Treatment and prevention
- Process: Systematic reviews and meta-analysis of randomized controlled trials. Library includes a database of randomized trials identified by the review groups and volunteers hand-searching the literature.
- Respiratory medicine topics represented: sleep apnea, COPD, mechanical ventilation, asthma. The library also includes a database of reviews about health technology assessment that includes lung reduction surgery, domiciliary oxygen for COPD, and pulmonary rehabilitation.

*MEDLINE (PubMed)*
- On-line: http://www.ncbi.nlm.nih.gov
- Abstracts only. Some links to journal web sites.
- Free service
- Focus: Unfocused
- Process: Every publication in 4,000 biomedical journals (11 million records)
- Respiratory medicine topics represented: All
- Search can be limited using methodological filters using Clinical Queries option (http://www.ncbi.nlm.nih.gov)

study showed that the quality of reviews has not improved in the last decade.[33]

The type of question and the topic would direct the evidence seeker to the appropriate evidence source. Searching, retrieving, and evaluating all the reports available is time consuming. Those pressed for time will find useful an increasing array of evidence summaries to answer common clinical problems (see Table 2).

Armed with the question, you begin with *Clinical Evidence* (see Table 2) but find that it does not contain information on pulmonary rehabilitation. A search of *Best Evidence* using the term "pulmonary rehabilitation" produces 4 hits: 1 meta-analysis of randomized trials[22] and 3 randomized trials, 2 of which were already included in the meta-analysis. A search in the Cochrane Library reveals one review of home interventions in COPD patients that excluded physical training.[34] A search of MEDLINE, through the PubMed interface, using the term "pulmonary rehabilitation" and limiting the search to randomized trials in adults published since 1995 (the time boundary of the meta-analysis) yields 30 articles, of which 7 appear to provide data relevant to the question.[35–41] A quick review of the abstracts associated with those articles reveals findings consistent with the results of the meta-analysis. Armed with that information you decide to review the meta-analysis.[22]

## The Appraisal

Over the last 10 years, the Evidence-Based Medicine Working Group has published (in *The Journal of the American Medical Association*) 25 Users' Guides to the Medical Literature.[9,42–73] We have expanded and updated these guides and have published them in a book.[74] These guides present 3 core questions the reader should ask when critically appraising a research report: Are the results valid? What are the results? Can I use the results in the care of my patients?

Guided by a set of criteria presented as questions, clinicians determine the validity of the results by determining the extent to which investigators have implemented methodological safeguards against bias. Each question addresses the presence of a source of bias, some empirically established, pertinent to each study type.[75]

The assessment of the results involves ascertaining the size of the effect and the precision of the effect estimate. For therapy questions, clinicians should look for the relative risk reduction, the risk difference, and the number-needed-to-treat.[76] Clinicians should examine the CIs to assess the range of values compatible with the results and determine if the interpretation of the findings changes at either of its limits. Though an exposition of measures of effect and of CIs is beyond the scope herein, interested readers can find guides to the interpretation of results in other sources.[74,77]

The final step involves determining how the results of the study apply to the type of patients seen in practice. This process involves making judgments about the magnitude of benefit and harm from the intervention, the extent to which the authors have addressed all patient-important outcomes, and the extent of the differences between usual patients and those involved in the study. With respect to the final point, clinicians must determine if differences are so great that the magnitude of benefits or harms is likely to differ substantially.[61] The differences could be biological (eg, different effects from a therapeutic agent in patients of different ethnic origin), socioeconomic (eg, no access to a costly agent), or behavioral, as we discussed above.

To critically appraise the meta-analysis of randomized trials of pulmonary rehabilitation by Lacasse et al,[22] we will follow the schema presented in the "Users' Guides" article addressing how to use an overview[50] and in the *Users' Guides* book.[74]

The meta-analysis starts by stating a focused question: what is the effect of pulmonary rehabilitation on exercise capacity and health-related quality of life in COPD patients? The authors included randomized trials of pulmonary rehabilitation versus conventional care in COPD patients (ratio of forced expiratory volume in the first second to forced vital capacity $< 0.7$ or forced expiratory volume in the first second $< 70\%$ of predicted), with the interventions lasting at least 4 weeks and reporting on measures of quality of life or exercise capacity. It is unlikely that authors missed important studies, given that they searched multiple electronic databases, reviewed the bibliographies of the included studies and pertinent meeting proceedings, contacted the authors of the trials, and contacted experts in search of unpublished material. Two reviewers appraised the validity of the trials and independently extracted data. These characteristics of the review suggest that the results are likely to be valid.

The results, which are similar from study to study, show important improvements in maximum exercise capacity and measures of quality of life (dyspnea and ability to cope with illness). The programs included in the meta-analysis were very different (with different intensities of intervention) but yielded consistent benefits, making generalization to other programs (and particularization to the program under evaluation in the case example) feasible.

The benefits achieved were of a magnitude that was perceived as important by patients: on average, patients allocated to pulmonary rehabilitation (compared to those allocated to usual care) walked 56 meters more in a 6-minute walk test, experienced less exertional dyspnea, and felt a better sense of coping with the disease and its manifestations. However, the review did not include other important

outcomes such as the costs of the programs, potential harm to the patients, and long-term benefits in terms of disability and mortality.

A PubMed search for economic analyses of pulmonary rehabilitation programs (see Table 2), using the search terms "pulmonary" or "respiratory rehabilitation" AND "cost-effectiveness analysis" and limited to randomized controlled trials, revealed 2 relevant studies: one by Goldstein et al[78] and another by Troosters et al.[40] The study by Goldstein evaluated the efficacy and costs of a 2-month in-patient rehabilitation program followed by a 4-month out-patient phase, compared to usual community care for patients with severe COPD. The investigators calculated costs from the societal viewpoint and included the costs of hospitalization, medical care, medications, home care services, assistive devices, and transportation costs and reported costs in 1989 Canadian dollars. The investigators measured health-related quality of life as the primary outcome of this randomized trial, using a validated questionnaire for COPD patients. Data on costs and health-related quality of life were integrated using a cost-effectiveness ratio and the cost per person multiplied by the number of people needed to treat to achieve small but important benefits in fatigue, dyspnea, emotional function, and coping with the disease. The study found the rehabilitation program to be expensive (Can$47,548 required for a single patient to achieve an important benefit in dyspnea). The in-patient phase (hotel and nursing) was responsible for most of the incremental costs, compared to usual community care. The costs of the out-patient phase compared favorably with usual community care, but its effectiveness alone was not assessed in the study.

The study by Troosters et al[40] evaluated the cost-effectiveness of a 6-month out-patient rehabilitation program in Belgium. The investigators calculated the total cost of the program per patient using the number of sessions attended and multiplying that number by the charges per session. The study found that an improvement of 52 meters in the 6-min walk test would cost $2,600 per patient. This analysis only considered charges reimbursed by the National Health Insurance and assumed that all patients would experience the same average benefit. Though the study is limited in that it did not calculate the cost per unit gained in terms that are meaningful to patients (such as the cost per patient who achieves an important benefit), the improvement in walk test is very close to that achieved both in the economic analysis by Goldstein et al[78] and in the studies included in the systematic review. Thus, the extent of patient-important benefit is likely to be similar.

### The Application

After considering the results from the meta-analysis and from the more recently published randomized trials that report on cost-effectiveness, your team reported back to the administration. The evidence suggested that pulmonary rehabilitation, such as the program delivered by the team, improves patients' exercise capacity, dyspnea, and ability to cope with COPD. The consistency of the findings in the meta-analysis and in the studies published subsequently suggest that similar clinical benefits could be realized across a broad range of practices and patients. Though the programs with a prolonged in-patient component appeared expensive, those operating in the out-patient setting seemed more cost-effective.

### Scenario Resolution

Simultaneously, the geriatricians conducted a similar process to identify and assess the evidence for geriatric day hospitals and presented their findings to the administrator. The administrator found the evidence for geriatric day hospital far less compelling than the evidence for pulmonary rehabilitation and decided to allocate funds to expand pulmonary rehabilitation.

## Summary

In summary, evidence-based medicine represents a paradigm shift in the way we learn and practice medicine. The practice of evidence-based medicine requires careful examination of the evidence, using a set of formal rules applied in an explicit manner, followed by its judicious application to decision-making, with an understanding of the patient context and values. We believe that this approach leads to optimal patient care. At the very least, evidence-based practice facilitates an explicit decision-making process that is transparent and thus open to evaluation and improvement.

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## Discussion

**Rowe:** Would you discuss how the recent evidence on the importance of blinding[1] is going to affect the quality assessment score that Jadad developed for judging the quality of a randomized controlled trial in a systematic review?[2] Also, when do you think there's enough evidence in systematic reviews? Our own experience has been that despite very rigorous attempts to produce systematic reviews that demonstrate efficacy in therapeutic interventions, people still don't believe the results. What is your strategy to deal with that?

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**Guyatt:** Alex Jadad some years ago developed a method of looking at the validity of randomized trials, and some of us think there were limitations of that right from the beginning, although it was definitely a good try. However, I don't think Alex or anybody else would pretend that that was going to be the definitive way of looking at the validity of randomized trials, which would be impervious to subsequent evidence and better ways of doing it. Clearly, this new finding makes it very problematic to simply look at the statement on double blinding, and, in fact, validity methods will have to take into consideration that there are 6 different groups that could be blinded and that clearly the greater the extent of blinding across those groups, the stronger the validity of the study. In terms of your second question, about when is evidence enough, can I just ask you—enough for what?

**Rowe:** Essentially, like your cumulative meta-analysis on thrombolytics: that's a lesson that we've learned. Now we're looking at cumulative meta-analyses and meta-analyses of therapies that show a benefit, and we're still not able to convince clinicians to adopt those practices, or to stop using harmful treatments.

**Guyatt:** There are 2 issues here, it seems to me. First, let's look at it on a rational basis. When should we conclude that a treatment certainly should be disseminated? When I say that, I'm implying the fact that there are strengths of evidence. It isn't either that the decision is *in* or the decision is *not in*; we should do it—we shouldn't do it. There's an accumulating evidence that people may quite reasonably have different thresholds as to when to adopt something, and that goes back to values or preferences. Our patient may be somebody who would like to try anything, even if it might not work, or the patient may be very conservative about taking medication and doesn't want to do it, doesn't want to risk harm, and will only take a medication if there is very strong evidence. Even for us as individual clinicians, because our patients differ, we're going to have different thresholds of when it's appropriate to administer a treatment for different patients. Second, it doesn't depend just on the evidence. It depends on things like the potential harms and costs associated with the treatment. So, clearly, our thresholds for adopting a treatment should differ on whether it has minimal side effects and minimal cost and we're prolonging the patient's life, versus it's very toxic and/or very costly and we're preventing the patient from having a runny nose. In those 2 contrasting situations you can have the same number of trials, the same relative risk reduction, and the same confidence interval, but the threshold will clearly differ for saying we have enough evidence to begin to apply it or we have enough evidence to strongly recommend that everybody apply it. Now that's rationality. A cardiologist coming back from a recent meeting told me that there was a recent trial that showed that the IIb/IIIa inhibitors probably did not reduce adverse outcomes in people who were presenting with acute ischemic syndromes. And all the cardiologists got up and said "Wait till the publication's out; we have to look very carefully at that. There may be something wrong with that trial." On the other hand, a recent report, single trial, big one, suggested that clopidogrel reduces adverse outcome events in people who were presenting with acute ischemic syndromes, given in addition to aspirin. Everybody walked out saying, "Yes, let's do it." People have entrenched biases, beliefs, and ways of doing things. We tend to be resistant to new evidence, and we're more receptive to some new things than others. If evidence contradicts our general mindset, we're going to be much more resistant. So when you're talking about changing behavior, evidence is one relatively small factor in chang

ing anybody's behavior, be it clinicians or other people. We have to look at other strategies of changing people's minds and, once we've changed their minds, other strategies for changing their behavior. So there's the rational part of it that we want to get right, and there is also the changing behavior part that we need to get right.

**Chatburn:** You mentioned the "*n* of 1" clinical trial. It seems to me that a key practical problem might be knowing when to stop. In normal clinical trials you can do a power analysis and calculate an appropriate sample size, and that would affect how long you would study. So is there an analogous approach for an *n* of 1 trial?

**Guyatt:** Yes, there is an analogous approach. If you really want to get sophisticated, you can look at the variability of your outcome measure and do a power analysis—the equivalent to the number of patients. Here it would be the number of pairs of treatment periods you undergo. That, even to me, seems like a bit of overkill. Here you can really individualize. Some patients may be willing to accept one pair: "Oh, I was better. Well that's enough for me. I'll take it." Others may be concerned with cost or may get headaches from the treatment, and even if it makes them less short of breath, they may want to have a stronger evidence before they agree to use the treatment over the long term. Typically, we encourage people to do 3 pairs. At the end of 3 pairs, we scientifically have strong evidence. We then review the results with the patient as we go along, and say, "OK, here are the results. Have we got an answer or not?" So it's very much a collaborative venture between the clinician and the patient, and, again, we recognize that the threshold of when you stop is, in fact, a value judgment.

**Rubenfeld:** I want to push a little further on your judgment that responding to internal biases is irrational. In fact, I'd like to submit that it's the height of rationalism and we're just perfect Bayesian thinkers.[1] All that evidence does is try to give us a likelihood ratio, which I think is problematic, as you've shown us that the same evidence meta-analyzed and looked at in different ways gives you different likelihood ratios over time. But how do we as evidence-based thinkers approach the problem that all we're doing is providing likelihood ratios to individual's priors. And your cardiologist has different priors for the effectiveness. We may say that's irrational, but weren't they really just acting like good rational Bayesians?

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**Guyatt:** We have a fundamentally different notion of human beings, you and I. When psychologists have studied it, if you tell people they have an 80% chance of surviving, they make different decisions than when you tell them they have a 20% chance of dying. That's just one example. Personally, I think the explanation had nothing to do with different priors. It had to do with how many dinners they'd had that were funded by the drug industry and how many consultancies they'd had with the drug industry.

**Rubenfeld:** I'm not sure that Bayes told us where priors were supposed to come from. Isn't it the problem that evidence itself doesn't tell us things about the world? If I told you that I see a unicorn outside—if I see it, I observe it, and draw it, and it's a very systematic observation, it's still not going to convince anyone that there are really unicorns in the world. But that's a systematic observation about the world. The reason we don't believe there's a unicorn out there is because we have a strong prior that unicorns don't exist. I just think that evidence doesn't speak with a single voice. As part of evidence-based medicine, we teach house staff how to think about prior probabilities and incorporating diagnostic evidence. And, really, all of this evidence is diagnostic: we're trying to diagnose the effectiveness of a drug. It seems to me we can't just dismiss the fact that people approach evidence with different priors. You can't just dismiss the whole concept of incorporating evidence into a post hoc probability by saying that all priors are irrational and we shouldn't begin with any prior probability about evidence.

**Guyatt:** I'm not trying to say that in the least. Indeed, I think we do think of priors, and although I'm personally so far unimpressed with Bayesian approaches to individual randomized trials or meta-analyses, I would nevertheless agree with you that prior probabilities are very important and influence our ultimate decisions and that we should look at them explicitly. I would certainly agree with that.

**Tonelli:** On the subject of hierarchies of knowledge: expert opinion doesn't appear on your hierarchy of evidence.

**Guyatt:** Expert opinion is not evidence.

**Tonelli:** And clinical experience is evidence?

**Guyatt:** Clinical experience is evidence. Let's distinguish: clinical experience is evidence; expert opinion is not evidence. In other words, if I say "Do it my way" that's not evidence. If I say "I have seen 100 patients and my observations with those 100 patients are such and such," that's evidence. It's weak and unsystematic, but it's evidence. But "Do it my way" is not evidence. I think that's an important distinction.

**Tonelli:** I think you have an interesting definition of expert opinion as a sort of unsubstantiated statement of medical authority.

**Guyatt:** No, that's not a definition—opinion is opinion. Evidence is a statement of observations one has made.

**Tonelli:** But doesn't opinion derive from experience?

**Guyatt:** Certainly one derives an opinion from the totality of the evidence. One derives an opinion from meta-analysis of randomized trials and from *n* of 1 trials. But opinion is not the same as evidence, and the two are worth distinguishing.

**Tonelli:** But if expert opinion derives from one's clinical experience, then you would put it somewhere in this hierarchy.

**Guyatt:** No, no. Opinion is never in the hierarchy of evidence. The hierarchy of evidence is about *evidence*, and opinion is something different. The processes of going from evidence to action, from evidence to recommendations (another way of saying that opinions are recommendations) involves summarizing the evidence in some appropriate way and then making explicit your values in going from your evidence to your recommendations. That process needs to be understood. The ultimate recommendation is not evidence, it's a recommendation. The 2 things are separate.

**Tonelli:** I guess, then, expert experience might fit somewhere in here.

**Guyatt:** Sure. Clinical experience of the expert is evidence. If an expert says "I've seen 100 people, and when I do it this way, this is what happens," that's evidence.

**Tonelli:** Regarding your description of the ascending or descending value of particular types of evidence, you seemed to say that once there's a higher level of evidence, then lower levels of evidence become meaningless. That is, once one has a systematic review of good randomized controlled trials, then clinical experience no longer enters into medical decision-making, or shouldn't enter into medical decision-making.

**Guyatt:** Well, remember it's the conscientious and judicious use of evidence. So it depends on what you mean. Despite all the expert opinion and expert experience that encainide and flecainide were good antiarrhythmic agents, once randomized trials showed those drugs kill people, then, to me, that expert opinion and experience was irrelevant.

**Tonelli:** Let me use an example. Say there is fairly convincing evidence from one randomized controlled trial favoring low-stretch ventilation in acute respiratory distress syndrome, but the physician says "Well, in this particular case, I'm not going to use low-stretch ventilation, because it seems that every time I let the pH drop to 7.25, this patient has arrhythmias, and I think arrhythmias in this situation are bad, so I'm going to go with a little higher ventilation." That physician would be using a physiologic argument that is subject to the biases you describe, but is it legitimate to use a physiologic argument to temper the application of a randomized controlled trial? Is it ever legitimate for physicians to use what you call lower levels of evidence in making those medical decisions?

**Guyatt:** Absolutely yes. In fact, it sounds to me like what you've just described is an *n* of 1 trial, though a relatively weak *n* of 1 trial. If in that individual every time we lower the tidal volume the patient gets arrhythmias, which look like they might be lethal, but every time we turn up the tidal volume they go away, you've just done an *n* of 1 trial with evidence specific to that individual.

**Tonelli:** But I'm only using physiologic rationale. I'm arguing from physiology here because I can't do an *n* of 1 trial.

**Guyatt:** You don't want to wait till they suffer ventricular fibrillation and you have to resuscitate—that's right. The point of this is, I haven't spent a lot of time on applicability, but to give another example in an area I work in, atrial fibrillation: anticoagulation reduces the stroke rate by two thirds, but if I have a patient who's falling and hitting his head every second day I'm not going to use anticoagulants. In other words, it's back to the point that all that randomized trials or meta-analysis can tell us about is average patients, but every patient doesn't respond in the same way and there may well be compelling reasons in the individual whereby they do not get the average response, and clinicians have to use all the levels of the evidence for that individual. In the situation you were describing, there are extremely compelling grounds to use higher tidal volumes.

**Durbin:** One concern I have is that when I read a meta-analysis, I have trouble identifying specifically how they excluded or included patients. Often they say "We researched the entire literature, including unpublished reports, to collect all the patients we could possibly find." The criteria are very explicitly stated, but are really very brief in the paper. It's hard to tell who got excluded from many of the studies or what studies were excluded and why. So when I read that, I have to accept the authors' understanding that this is truly representative of what I'm interested in. Second, there's a publishing bias to publish only studies that have positive results—either positively negative or positively pos-

itive. So there's a whole wealth of studies out there that we really don't have good access to. Sometimes some of them are included because of special knowledge the authors have, but oftentimes they're not. I worry that that influences the results. If I have a well-described randomized prospective controlled study, I can tell what patients are in it or how the study was done, but I don't have that same degree of confidence in meta-analyses. What are your comments about that problem?

**Guyatt:** First of all, what are the alternatives? We happen to pick the 2 or 3 trials that we're particularly fond of. That's the usual clinical approach. As far as I can see, the systematic review has to be better than a haphazard selection of trials that we're fond of. So the issue isn't whether we should use systematic reviews, but how to make them better. How do we make them better? We look hard for unpublished material and make an effort to get at that unpublished material and get around that publication bias as part of the optimal systematic review. Second, we hopefully will move more and more to electronic sources where we don't have the limitations of journals—that they squeeze your article and some of the information you are interested in is omitted. And in an electronic world the author's e-mail address should be available. If you are really interested enough to know why they excluded a certain trial or what they did, you should be able to go to the people who did it and find out the information.

# Outcomes Research in Respiratory Care

Robert L Chatburn RRT FAARC

Introduction
A Brief History
Understanding the Jargon
Outcomes Research: Focus and Methods
The Outcome of Outcomes Research
Examples from Respiratory Care
Summary

**Outcomes research seeks to understand the end results of particular health care interventions. End results include effects that people experience and care about, such as change in ability to function. The modern outcomes movement in the United States had its beginnings in the early 1980s, with an official start when Congress created the Agency for Health Care Policy and Research in 1989. Today known as the Agency for Healthcare Research and Quality, this agency supports outcomes research that is designed to answer 4 questions: (1) What works? (2) What doesn't? (3) When in the course of illness does it work or not? and (4) At what cost? Outcomes research provides the data for evidence-based medicine. Both activities work together in a continuous quality improvement cycle under the general heading of disease management. Outcomes research includes such things as epidemiology studies, clinical trials (designed as effectiveness studies), quality of life surveys, and cost analyses. Outcomes research is distinguished from traditional clinical research more by its focus than its methods. For example, outcomes research is population-centered rather than disease-centered, deals more with processes of care than drugs and devices, and relies less on the "hard sciences" such as physics and biochemistry and more on the social sciences such as economics, behavioral sciences, and epidemiology. Appropriate outcomes measures may be classified as (A) clinical, such as physiologic measures and mortality; (B) economic, such as direct and indirect costs of care; or (C) humanistic, such as quality of life and patient satisfaction with care. Respiratory therapists need to be familiar with outcomes research issues in order to be educated consumers of (and to participate in) future studies.** *Key words: evidence-based medicine, outcomes, respiratory.* [Respir Care 2001;46(11):1215–1223]

> In attempting to arrive at the truth, I have applied everywhere for information, but in scarcely an instance have I been able to obtain hospital records fit for any purpose of comparison. If they could be obtained, they would enable us to decide many . . . questions . . . . They would show subscribers how their money was being spent, what amount of good was really being done with it, or whether the money was not doing mischief rather than good.
>
> Florence Nightingale, *Notes on a Hospital*, 1873

## Introduction

As in other areas of medicine, outcomes research is starting to make its mark in defining optimal respiratory care practices.[1] With the need for cost containment, outcomes research becomes a double-edged sword, used both

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A version of this paper was presented by Mr Chatburn during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20–22, 2001, Banff, Alberta, Canada.

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to cut nonessential practices and to protect those that maintain quality of care. The profession of respiratory care has a long history of research and a commitment to basing practice on science. However, much of the research published in our field is still focused on devices and procedures rather than on the broader issues of patient outcomes and economic effects. We need to evolve our paradigm to accommodate the larger vision of disease management, which encompasses the arenas of outcomes research and evidence-based medical practice.

Herein I will give a brief history of the outcomes research movement, to provide some sense of context. Then I will try to demystify the language of outcomes research and review some of its themes and methods. Finally, I will present specific examples of outcomes research found in the pages of Respiratory Care Journal. Hopefully, these examples will illustrate some of the methods of outcomes research and stimulate future studies.

## A Brief History

Florence Nightengale may have been the first outcomes researcher in medicine. She had a flair for collecting, analyzing, and presenting data. She even invented the polar-area chart, where the statistic being represented is proportional to the area of a wedge in a circular diagram.[2] Yet, as the quote above indicates, she had as much trouble finding appropriate data as we do today. And, like modern times, there was much opposition to the reforms Nightengale proposed. Nevertheless, her most effective weapon was the presentation of solid, relevant data. For example, she showed "... that 'those who fell before Sebastopol by disease were above 7 times the number who fell by the enemy.' The opposition could not respond to her statistics and publication of the statistics led to public outcry."[2]

The modern outcomes movement in the United States had its beginnings in the early 1980s. The increasing focus on cost containment led to interest in identifying and eliminating unnecessary procedures. Perhaps more intriguing was the recognition that there were substantial differences in medical practice, apparently based on geography or race.[3–5] Indeed, some researchers claimed that "geography was destiny" because medical practices as commonplace as hysterectomy and hernia repair were performed much more frequently in some areas than in others, with no differences in the underlying rates of disease.[6]

Given those differences in practice and outcomes, it is logical to assume that some practices produce better outcomes than others. So the stage was set to improve efficiency and quality if only the right data were available. But where to look? The Office of Technology Assessment estimated that only 10–20% of interventions by physicians have been clearly shown in randomized clinical trials to be of value.[7] This is not surprising, given that clinical trials can cost millions of dollars and last years. Some suggested that data collected for administrative or billing purposes (eg, Medicare and Medicaid tapes collected by the Health Care Financing Administration) might contain valuable outcome data such as mortality, length of hospital stay, resource use, and costs. On the one hand, such data can be quickly analyzed, without requiring patient consent or interfering with medical care. On the other hand, critics argued that this type of research is limited by the quality and completeness of the data.[8]

It thus became evident that new data must be collected in a systematic fashion, with a specific focus on outcomes. In 1989 Congress created the Agency for Health Care Policy and Research (AHCPR). It consisted of 11 major components, including the Center for Outcomes and Effectiveness Research, the Center for Cost and Financing Studies, and the Center for Quality Measurement and Improvement. The initial focus of the AHCPR was to create Patient Outcomes Research Teams (PORTs—5-year studies of specifically identified diseases, with highly focused methods), the Pharmaceutical Outcomes Research Program, and the Minority Health Research Centers. In time, the AHCPR changed its name and its focus. Today, as the Agency for Healthcare Research and Quality, the focus is on "translating research into practice," creating Excellence Centers for Eliminating Disparities (based on race and ethnicity), and supporting the Centers for Education and Research on Therapeutics. According to the Agency for Healthcare Research and Quality[6], the purpose of outcomes research is to answer 4 basic questions:

- What works?
- What doesn't?
- When in the course of an illness does it work or not?
- At what cost?

These questions suggest the scope and focus of modern outcomes research.

## Understanding the Jargon

Like any new discipline, the field of outcomes research suffers from a lack of consistent definitions and unifying conceptual framework. Many seemingly unrelated terms are encountered in the literature, such as efficacy, effectiveness, quality of life, patient-centered care, and evidence-based medicine. All these terms signify a paradigm shift in which the emphasis is on populations rather than individuals, on practice guidelines rather than anecdotal justifications for treatment, and on capitation rather than fee-for-service payments. I have found it helpful to view this new paradigm in terms of the general concept of "disease management"[9] within which the specific activities of

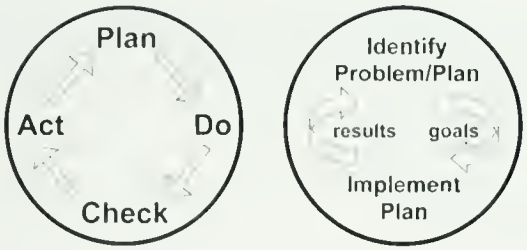


Fig. 1. Continuous quality improvement expressed in the traditional format of a cycle of "plan, do, check, act" and an equivalent cycle showing the interaction of plans and implementations through goals and measured results.[10]

outcomes research and evidence-based medicine interact in a process of continuous quality improvement.

*Disease management* (also called outcomes management) can be defined as the systematic, population-based approach to identifying patients at risk, intervening with specific programs, and measuring outcomes.[9] The basic premise of disease management is that there is an optimal strategy for reduced cost and better outcomes. Its emphasis is on identifying populations of interest, creating comprehensive interventions, explicitly defining and measuring outcomes, and providing a strategy for continuous quality improvement.

*Continuous quality improvement* is a cycle of activities focused on identifying problems or opportunities, creating and implementing plans, and using outcomes analysis to redefine problems and opportunities. Continuous quality improvement was started decades ago by pioneers such as Walter Shewart, W Edwards Deming, and Joseph Juran, and is currently embraced by the Joint Commission on Accreditation of Healthcare Organizations. The "*Plan, Do, Check, Act*" cycle (Fig. 1)[10] endorsed by that commission can be viewed as simply creating plans and implementing them. The plan leads to implementation through the creation of specific goals. Implementation leads to more plans through the analysis of results.

*Outcomes research* can be defined as the scientific study of the results of diverse therapies used for particular diseases, conditions, or illnesses. The specific goals of this type of research are to create treatment guidelines, document treatment effectiveness, and to study the effect of reimbursement policies on outcomes.[11]

*Evidence-based medicine* is an approach to practice and teaching that integrates pathophysiologic rationale, caregiver experience, and patient preferences with valid and current clinical research evidence. To implement evidence-based medicine, the practitioner must be able to define the patient problem, search and critically appraise data from the literature, and then decide whether and how to use the information in practice.[12]

If we view disease management as a universe of activities, then outcomes research (eg, epidemiological studies,

Fig. 2. Disease management expressed as a continuous quality improvement cycle showing the interaction of plans (created by research outcomes studies) and implementations (evidence-based medicine tools) through goals (desired outcomes) and measured results (actual outcomes).

clinical trials, quality of life surveys, efficacy and effectiveness studies, and cost analyses) and evidence-based medicine (eg, creation and use of practice guidelines and care paths) can be seen as subset activities linked by the general structure of continuous quality improvement (Fig. 2).

### Outcomes Research: Focus and Methods

Outcomes research can be distinguished from traditional clinical research more by its focus than by its methods. This difference in focus is highlighted in Table 1.[13] Ap-

Table 1. Differences in Focus Between Traditional Clinical Research and Outcomes Research

| Traditional Clinical Research | Outcomes Research |
|---|---|
| Disease-centered | Patient and community-centered |
| Drugs and devices | Processes and delivery of care |
| Experimental | Observational |
| Methods from "hard sciences" (physics, biochemistry) | Methods from "social sciences" (economics, behavioral sciences, epidemiology) |
| Efficacy | Effectiveness |
| Mechanisms of disease | Consequences of disease on patients |
| Effects of biochemical and physiologic factors | Effects of socioeconomic factors |

Table 2. Various Types of Outcome Measures Used in Outcomes Research

| Category | Type | Example |
|---|---|---|
| Clinical | Clinical events | Myocardial infarction |
| | Physiologic measures | Pulmonary function indices |
| | Mortality | Asthma deaths |
| Economic | Direct medical costs | Hospital and outpatient visits |
| | Indirect costs | Work loss, restricted activity days |
| Humanistic | Symptoms | Dyspnea scores |
| | Quality of life | Medical Outcomes Study Short Form 36 Questionnaire, St George's Respiratory Questionnaire |
| | Functional status | Activities of daily living |
| | Patient satisfaction | Cleveland Health Quality Coalition |

Table 3. Methods Used in Outcomes Research

| |
|---|
| Qualitative methods (formal hypothesis testing not necessarily required) |
| Generate hypotheses |
| Describe complex phenomena |
| Identify relevance of findings to specific patient groups |
| Quantitative Methods |
| Experimental |
| Randomized controlled trials |
| Non-experimental |
| Data synthesis |
| Meta-analysis |
| Decision analysis |
| Economic analysis |
| Observational studies |
| Cohort |
| Case-control |
| Survey |

propriate outcomes can be grouped roughly into 3 categories: clinical, economic, and humanistic (Table 2).[9]

Outcomes research uses a variety of techniques (Table 3).[13] *Qualitative research* often produces large amounts of textual data in the form of transcripts and observational field notes. Rather than trying to identify a statistically representative set of observations, qualitative research uses analytical categories to describe and explain social phenomena.[14] Qualitative research generates hypotheses (although not necessarily hypothesis tests) and attempts to identify the relevance of findings to specific groups of people.[13]

*Quantitative research* uses both experimental and non-experimental designs. The classic experimental design of the randomized controlled trial can be applied to outcomes research if it is set up to evaluate effectiveness (as opposed to efficacy, see definitions below). Nonexperimental designs can focus either on data synthesis or observational study designs.

In keeping with the population-based theme of outcomes research, methods are needed to synthesize data from many studies, as opposed to interpreting the results of a single study. One such method is called *meta-analysis*.[15] The National Library of Medicine defines meta-analysis as follows:

> A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions that may be used to evaluate therapeutic effectiveness, plan new studies, etc, with application chiefly in the areas of research and medicine. The method consists of 4 steps: (1) a thorough literature review, (2) calculation of an effect size for each study, (3) determination of a composite effect size from the weighted combination of individual effect sizes, (4) calculation of a fail-safe number (number of unpublished results) to assess the certainty of the composite size.[16]

For an excellent introduction to meta-analysis (complete with an annotated bibliography), see the article by Arthur Jones that appeared in this journal.[17]

*Decision analysis* is used to determine optimal strategies when there are several alternative actions and an uncertain or risk-filled pattern of future events.[18,19] This technique is a derivative of operations research and game theory. It involves identifying all available choices and the potential outcomes of each. Usually a model is created in the form of a decision tree. The tree is used to represent the strategies available to the clinician and the likelihood that each outcome will occur if a particular strategy is chosen. The relative value of each outcome can also be described.[20,21]

There are several basic types of economic evaluation that are applied to health issues.[20,22] *Cost identification* is simply the description of the costs of providing the intervention. It is the first step in all the other types of analysis, but is often the only one reported in a study. *Cost of illness* analysis estimates the total cost of a disease or disability to society (eg, heart disease costs the United States $128 billion per year). *Cost minimization* is applied when 2 or more interventions are being compared on the same outcomes and the outcomes seem to yield similar effectiveness. Then the question is simply which is least expensive. An example would be the question of whether to repair or replace a mechanical ventilator. When the same outcomes are measured but the effectiveness differs, then they are compared on the basis of cost per outcome (eg, dollars per life saved or dollars per additional year of life) using *cost*

*effectiveness* analysis. If both outcomes and effectiveness differ, then a *cost-benefit analysis* first attempts to express both outcomes and benefits in terms of dollars. Then the interventions are evaluated in terms of the overall economic tradeoffs among them. In that way the cost of, say, a smoking prevention program can be compared to that of lung reduction surgery and both can be compared to other programs, such as highway development or job training. *Cost utility* analysis is similar to cost effectiveness except that the effectiveness is expressed as a "utility," which is the product of a clinical outcome (such as years of life saved), and a subjective weighing of the quality of life to be had during those years. Utility is often expressed as quality-adjusted life years (QALYs). For example, quality of life is often measured on a linear scale where 0 indicates death (or indifference to death) and 1.0 represents perfect health. Suppose a patient is discharged to a long-term ventilator weaning facility for 6 months and dies on the ventilator. If the patient rates the utility of life on the ventilator as 0.2, the patient has experienced $0.5 \times 0.2 = 0.1$ QALYs. If the assumptions are correct, this means that 6 months on a ventilator in a weaning facility is approximately equal in value to the patient as about 5 weeks (0.1 year) in perfect health. Economic analyses can seem overly complicated. For a very readable introduction written in the style of a conversation between 2 doctors, see the article by Eddy.[23]

Quality of life (QOL) measures have been important in research since the 1970s. Uses of QOL data include distinguishing patients or groups, evaluating therapeutic interventions, and predicting patient outcomes. However, there are many QOL instruments and much theory but no unified measurement approach. And there is little agreement on definitions and interpretations. Gill and Feinstein provide an excellent review of the issues, with recommendations based on a survey of published QOL data.[24] They argue that because QOL is a uniquely personal perspective, patient-specific measures should be used.

Another issue that seems confusing is the difference between efficacy studies and effectiveness studies. An *efficacy* study attempts to answer the question, "Does the intervention work in a tertiary care setting with carefully selected patients under tightly controlled conditions?" This type of study generally requires a priori hypotheses, randomization of subjects to predefined treatments, homogeneous patient populations at high risk for the outcome, experienced investigators following a specific protocol, a comparative intervention (eg, a placebo), and intensive follow-up.[9] Conclusions from this type of study prompt relatively high levels of confidence. However, because the design is so restrictive, the results may not be generalizable to a broad range of patients in usual practice settings. Thus, efficacy studies may not be appropriate for cost-effectiveness analyses.

In contrast, *effectiveness* studies are designed to answer the question, "Does the intervention work in clinical practice settings with unselected patients, typical care providers, and usual procedures?" Many effectiveness studies have been conducted as observational (often retrospective) studies in which observed groups were not randomly assigned and neither patients nor providers knew they were being studied. The weakness of this study design is that selection bias may be a problem (ie, the groups may not have the same prevalence of confounding variables), so adjustment for factors such as severity of illness and case mix becomes important. Prospective effectiveness trials have been reported.[25,26] They differ from typical clinical trials in that they enroll heterogeneous participants, impose few protocol-driven interventions, and report outcome measures relevant to the delivery system.[9]

## The Outcome of Outcomes Research

The Lewin Group has created a report of outcomes and effectiveness research at the AHCPR that describes the accomplishments and lessons of the past decade.[27] The report describes a conceptual framework for understanding and communicating the impact of outcomes and effectiveness research on health care practice. Four levels of impact are defined:

1. Findings that contribute to but do not alone reflect a direct change in policy or practice, such as new analytic methods or outcome instruments
2. Research that prompts the creation of a new policy or program, such as an American Association for Respiratory Care Clinical Practice Guidelines
3. A change in what clinicians or patients do, and
4. Actual changes in health outcomes

A survey was mailed to all principal investigators funded by AHCPR's Center for Outcomes and Effectiveness Research between 1989 and 1997. The results suggest that principal investigators have been most successful in (A) providing detailed descriptions of what actually occurs in health care, (B) developing tools for measuring costs of care and patient-reported outcomes, and (C) identifying topics for future research. Few principal investigators reported findings that provide definitive information about the relative superiority of one treatment strategy over another. Furthermore, there were few examples of findings that have been incorporated into policy (level 2 impacts) or clinical decisions (level 3), or into interventions that have measurably improved quality or decreased costs of care (level 4). The summary of the report concludes that "*One of the main challenges for the next generation of outcomes studies is to move from description and methods development to problem solving and quality improvement.*"

Not everyone believes that outcomes research is a good thing. Sandra Tanenbaum voices both practical and philosophical arguments against the outcomes movement.[28] She claims the outcomes movement exaggerates its usefulness by understating several difficulties. For example, how much time and money will be required to determine the effectiveness of many commonly used (and continuously evolving) medical procedures? How will physicians use outcomes data when making multiple consecutive decisions in the rush of daily patient care? And how will compliance with practice guidelines be enforced? Greco and Eisenberg cite references suggesting that clinical practice guidelines have been remarkably unsuccessful in influencing physician behavior.[29] Reasons they describe for this include the fact that some guidelines are not written for practicing physicians, the issue of physician disagreement with or distrust of guidelines written by so-called national experts, and physicians choosing to ignore guidelines because of nonclinical factors such as financial incentives or fear of malpractice litigation. Woolf et al[30] believe that the most important limitation of guidelines is that the recommendations may be wrong. These authors cite 3 reasons:

1. Scientific evidence about what to recommend is often lacking, misleading, or misinterpreted.

2. Recommendations are influenced by the opinions of the guideline development group, but the value judgment of the group may be the wrong choice for individual patients.

3. Practices that are suboptimal from the patient's perspective may be recommended to help control costs, serve societal needs, or protect special interest groups.

Furthermore, the promotion of flawed guidelines can encourage if not institutionalize the delivery of ineffective, harmful, or wasteful care.[1]

Haycox et al contend, "Guidelines generate systematic and paternalistic pressure for the many to conform to the views of the few."[31] These authors point out that the universal aim of clinical guidelines (ie, to promote "best practices" that improve the outcomes of treatment) rests on 2 assumptions. The first is that outcomes identified in clinical trials are reproducible in normal practice. The second is that rapid and universal adoption of an effective treatment leads to optimal treatment for the whole population. Unfortunately, in real life clinical practice, resources are restricted and patient compliance is less reliable, so the anticipated benefits are rarely fully realized.[2] An excellent review of practice guidelines, with references to studies of their efficacy, can be found at the World Wide Web site of the Agency for Healthcare Research and Quality.[32]

I have noticed something in reading the arguments for and against outcomes research, practice guidelines, and evidence-based medicine in general: though all of the arguments seem to have elements of truth, the arguments *against* are less organized, appear to be reactionary, and overlook the fact that the very same weaknesses apply to decisions by individuals (ie, clinicians customizing treatment for specific patients) as to those generated by a group (ie, treatment using practice guidelines). The arguments *for* evidence-based medicine, on the other hand, are elegantly worked out in great detail, using every helpful tool from common sense to formal decision theory. One outstanding example is the recent textbook edited by Guyatt and Rennie.[33] One need only flip through the 706 pages of that seminal work to be convinced of the solid theoretical framework advocated by those in favor of evidence-based medicine. You won't find a comparable book arguing for the status quo.

## Examples from RESPIRATORY CARE

Kollef[1] has suggested that outcomes research, along with its methodologies and core curriculum,[34] be viewed as an important discipline for the field of respiratory care. Specific areas in which outcomes research techniques could be employed include:[35]

1. Determining the effectiveness of continuous quality improvement initiatives

2. Comparing differences in respiratory care practice in order to identify optimum strategies

3. Developing and assessing innovations, and

4. Evaluating resource utilization in areas employing respiratory therapists, compared to similar settings without them

Indeed, this journal has published a good deal of outcomes research in the last few years. A quick survey of articles in the Original Contributions category from 1997 through 2000 showed that about 28% of articles could be classified as outcomes research (Table 4). Though the majority of articles are still focused on devices and procedures, a number of those that focused on problem solving and quality improvement serve as examples. What follows is a brief description of the methodology used in a few of those studies.

Table 4. Percent of Original Contributions Published in RESPIRATORY CARE Journal That Qualify as Outcomes Research*

| Year | % |
|---|---|
| 1997 | 4 |
| 1998 | 53 |
| 1999 | 41 |
| 2000 | 13 |

*The overall average was 28%.

1. Stoller JK, Orens D, Ahmad M. Changing patterns of respiratory care service use in the era of respiratory care protocols: an observational study.[36]

This was an observational study that qualifies as outcomes research because it was an evaluation of clinical outcomes in a "real world" setting during variations in respiratory therapy practices. The authors hypothesized that the use of a respiratory therapy consult service would decrease over-ordering of respiratory care services and decrease the volume of respiratory care services delivered. Data were obtained from the departmental management information system (Clinivision, Puritan-Bennett) and from the hospital's cost management software (Transitions Systems). They compared baseline data from 1991 (prior to establishment of a respiratory therapy consult service in 1992) to clinical data from 1996. Results were reported using descriptive statistics (averages, percentages, and trend graphs) of numbers of therapies, numbers of patients treated, and costs of therapies.

2. Adams AB, Shapiro R, Marini JJ. Changing prevalence of chronically ventilator-assisted individuals in Minnesota: increases, characteristics, and the use of noninvasive ventilation.[37]

This was an epidemiological study. Such studies describe the distribution and size (prevalence and incidence) of disease problems in human populations. The authors developed a study question: Did cost constraints and changes in care settings and techniques affect the number of ventilator-assisted individuals, their sites of care, or methods used for ventilatory assistance? They defined ventilator-assisted individuals and specified inclusion/exclusion criteria. Data were generated from surveys sent to all sites providing care for ventilator-assisted individuals. Results were reported using descriptive statistics (averages, medians, percentages, and bar graphs) numbers of patients treated and diagnostic categories.

3. Myers TR, Chatburn RL, Kercsmar CM. A pediatric asthma unit staffed by respiratory therapists demonstrate positive clinical and financial outcomes.[38]

This was a controlled clinical trial designed as an effectiveness study (ie, a heterogenous patient population treated by usual caregivers in a standard acute care environment). The authors tested the hypothesis that using respiratory therapists in a disease management model using a dedicated asthma unit and a standardized treatment protocol would improve efficiency of care, compared to the historical method of random placement of patients with care dictated by individual physician preference. An algorithmic treatment protocol was defined. Patients treated by protocol were compared to historical controls. Data were obtained from patient charts and the hospital information system. Outcomes were stratified by an asthma severity index. Results were reported using inferential statistics to compare hospital length of stay, cost/case, and care path differences. Nonparametric tests were used to assure the comparability of the 2 treatment groups on confounding factors such as age, race, and distribution of disease severity.

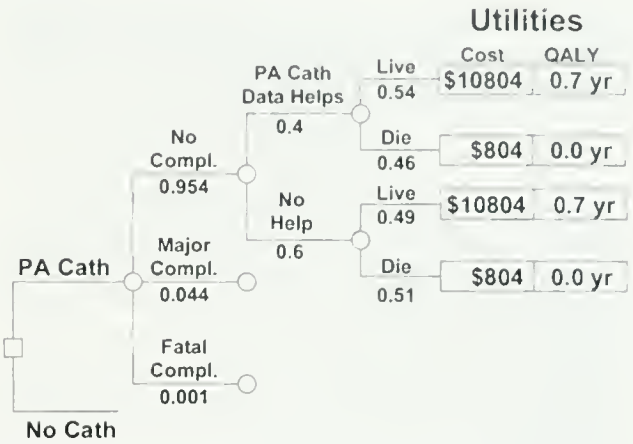


Fig. 3. A portion of the decision tree used in a cost-utility study by Smith and Pesce.[38] The model includes baseline values for probabilities, costs, and quality-adjusted life years (QALY). Probabilities are expressed as decimal numbers below the tree branch labels. The square node represents the decision whether to perform pulmonary artery catheterization (PA Cath) or not (no Cath). The circular nodes denote the possible outcomes from that decision (only some are shown). QALY is calculated for patients who survive hospitalization by multiplying the life expectancy of those patients (1.74 years) by their quality-of-life utility value (0.4, taken from the literature). Compl. = complications.

4. Parker L, Walker W. Effects of a pulmonary rehabilitation program on physiologic measures, quality of life, and resource utilization in a health maintenance organization setting.[39]

This study provides a good example of how to assess QOL issues. The researchers created a priori hypotheses and described the study population based on diagnosis and physiologic measures. They defined the intervention as rehabilitation classes at a specific frequency and duration along with an exercise program. Their QOL survey was abstracted from other published, validated QOL instruments. They used inferential statistics to compare charges and QOL scores. Results were reported using graphs and mean values.

5. Smith KJ, Pesce RR. Pulmonary artery catheterization in exacerbations of chronic obstructive pulmonary disease requiring mechanical ventilation: a cost-effectiveness analysis.[40]

Despite its title, this study is an example of cost-utility analysis, as I have defined it above, because the results are expressed in terms of patient utility (using a QOL score on a scale of 0 = death to 1.0 = perfect health) and QALYs. This article provides an excellent description of a complex topic, showing how a decision tree model is constructed (Fig. 3), how probabilities of different outcomes are estimated, how costs are attributed, and how utility is calcu-

lated. In addition, it provides an example of how sensitivity analysis is used to evaluate the effects of various baseline values (ie, assumptions) within the model.

## Summary

Outcomes research seeks to understand the end results of particular health care interventions. End results include effects that people experience and care about, such as change in ability to function. In particular, for individuals with chronic conditions in which cure is not always possible, end results include quality of life as well as mortality. By linking the care people get to the outcomes they experience, outcomes research has become the key to developing better ways to monitor and improve the quality of care.[6]

The methods of outcomes research differ substantially from those of traditional clinical research. Respiratory therapists need to be familiar with these methods to be educated consumers of (and to participate in) future studies. Readers interested in learning more about outcomes research are encouraged to read the annotated bibliography of key articles by Piccirillo et al.[11]

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## Discussion

**Rubenfeld:** Could you go back to the slide that showed a conceptual model of evidence-based medicine and outcomes research. I agree these terms are problematic. They certainly confuse me. It seems we ought to make sure we all are on the same page.

**Chatburn:** Do you buy that or not?

**Rubenfeld:** I don't know. I have some problem with having a little box underneath evidence-based medicine that says "practice guidelines and care paths." I actually think that's one of the tar babies that evidence-based medicine has gotten stuck with. I wonder if that's correct, that that box belongs next to evidence-based medicine?

**Chatburn:** I meant this slide to express that, if you're going to think of outcomes research as a way of identifying problems and opportunities, then evidence-based medicine is associated with the creation and implementation of plans for improvement. It wasn't meant to suggest that that's all evidence-based medicine is.

**Rubenfeld:** I don't know. I wonder whether other people here think it even belongs, whether practice guidelines and care paths should be in a box off to the side that talks about how to get it into practice once you have the evidence-based medicine recommendations.

**Hess:** Are not practice guidelines a way of operationalizing evidence-based medicine? Is that a correct or incorrect way?

**Guyatt:** Practice guidelines can be a way of operationalizing evidence-based medicine or a way of operationalizing non-evidence-based medicine. In other words, part of our *Users' Guides*[1] are guidelines for looking at practice guidelines. Most practice guidelines developed now are still very deficient, and almost all of them are totally deficient in terms of the principle of evidence-based practice that evidence never tells you what to do. It's evidence and values, and values should be made explicit. Very very seldom do guidelines make their values explicit.

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**Rubenfeld:** So you may have some issues with this at least geographic linkage of these concepts?

**Guyatt:** Yes. The practice guidelines and care paths are one way of implementing evidence-based practice. They can be well done or badly done, and, up to now, very few have met rigorous standards.

**Ellrodt:** I've struggled with this for a long time. What you haven't thrown in here—just to totally muddy the waters—are health services research and applied health services research, which really messes it up. I'm kind of looking at all these terms like beauty in the eyes of the beholder. Everybody you talk to has a different definition, depending on what they do. I'm not sure how to operationalize this. When I'm totally confused, I either form a task force or draw a bad diagram. I've tried to vend this one out, and that doesn't work very well. I'm not sure what it is, and, you know, we could probably spend the next 2 days discussing what we think outcomes research is, but I don't think that'll get us there.

This is probably as useful as any construct. I think the key is to have a construct in some way that allows you to figure out where things fall and then allows you to develop priorities from the construct. I would argue that this then allows you to act on those. What you heard from the Agency for Healthcare Research and Quality was that it's time to take some of these issues and expressions of evidence and act on them; I think that is the big missing piece.

Gordon [Guyatt] very nicely got to that issue about integrating with patient values. We tend, unfortunately, to think of evidence-based medicine as merely the elucidation of the power of the evidence or the strength of the evidence. We don't think of it more broadly, as Gordon has tried to remind us, as really the practice—integrating that information into patient values, acting on it, and seeing if it actually worked. There's another loop to the whole thing. I think that at some point whatever your construct is, as long as there's some way to get out of the circle and into action, I think it will probably work just fine.

**Guyatt:** Just to clarify, you made the contrast between randomized trials

focusing on efficacy and observational studies focusing on effectiveness or management, and then in what I would say is a more enlightened way, you identified randomized trials that can focus on effectiveness or management. Rather than make the dichotomy of explanatory randomized trials and effectiveness or management/observational studies, I would say we need to move toward management studies, but with randomized trials that address management issues as well as observational studies, and we will end up with much stronger inferences.

The other controversy I would like to label is as follows. Gray [Ellrodt] just said that we do our randomized trials but must find out if the interventions work in practice. Some of us, and I would certainly be in this camp, would say that if the apparent effectiveness is different in clinical practice than it was in randomized trials, you never know whether that's due to different populations at the start or whether the treatment really works differently. That realization leads to a different approach to optimizing practice, in which we get our information on what works and how it works from management randomized trials, and from there rely on quality assurance—making sure that people apply the interventions we know work in clinical practice.

In other words, the evaluation should be more process-oriented. So that is an alternative strategy, and one could argue about where the balance should be, but our argument would be that the assessment of outcome should come from randomized trials, and one then focuses on ensuring that the process suggested by those randomized trials is followed in practice.

**Chatburn:** Exactly. In my experience, it's one thing to know the right thing to do and another thing entirely to do it and to objectively measure that you are doing it.

**Mishoe:** I agree with Gray [Ellrodt] that conceptualization in terminology really complicates all of our topics and issues today, and we could be here for a couple more days, but I would like to go back to Gordon Rubenfeld's point that, for purposes of this Journal conference, I would hope to clarify some of these topics for the average practitioner. I work with a lot of medical students and respiratory care students, and I think we do them a disservice when we lump together practice guidelines with evidence-based medicine, because the novice believes that is evidence, when they have a practice guideline. For the purpose of this conference, if we could agree to not doing that, I think it would be helpful to the published papers.

**Pierson:*** Rob [Chatburn]'s discussion about what are the appropriate outcomes for respiratory care research prompts me to come back to Dr Guyatt's hierarchy of evidence, specifically the *n* of 1 trial, which troubles me a bit, and I guess it's because sometimes there's a temptation to use that as a kind of a loophole around evidence-based medicine.

Say I have a patient with acute respiratory distress syndrome and when I turn the patient prone his partial pressure of oxygen goes up, when I turn the patient back it goes back down, and when I turn the patient prone again it goes back up again. Haven't I just done an *n* of 1 study? And therefore am I not justified in using that therapy? To heck with your randomized controlled trials and your meta-analyses.

This is deliberately a perversion of it, but I'm worried a little bit about Dr Guyatt's statement that you can move an *n* of 1 trial up to the head of the list and even put it ahead of those more elegant and formalized things if you're dealing with an individual patient and you have something that works in that patient.

**Guyatt:** First, I'd like to say thanks very much. That's an excellent observation. What we need to do is separate our study design from the outcomes being measured. The *n* of 1 trial is at the top of the hierarchy when it measures what I would call a "patient-important outcome," that is, the outcome of this *n* of 1 trial. So if at the end of an *n* of 1 trial with a patient with chronic obstructive pulmonary disease you find out that giving beta agonists or theophylline or whatever makes the patient feel better, you have a definitive *n* of 1 trial. If you substitute a physiologic end point such as oxygenation, then in your *n* of 1 trial you've shown that for that patient, his oxygenation might improve. But if you ask the patient "Would you like your oxygenation improved? You won't live any longer and you won't feel any better, but your oxygenation will be improved," most people would decline that therapy.

So we must distinguish between the study design and the outcome being measured. And I could not agree more that if in making an *n* of 1 trial we equate that with a substitution of physiologic end points versus randomized trial of patient-important outcomes, we'd be making a big mistake. I think that's an excellent point.

**Chatburn:** Your key phrase was "for that patient." Do you find people trying to generalize to other patients when, indeed it should only be applied to that patient at that time?

**Guyatt:** You mean from an *n* of 1 trial?

**Chatburn:** Yes.

**Guyatt:** Well, sure. In a sense, clinical experience is weak *n* of 1 trials. So you can have *n* of 1 trials that are

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weak and *n* of 1 trials that are strong. People are trying to generalize from inadequate samples all the time.

**Tonelli:** I like the fact that you put *n* of 1 trials at the head of the hierarchy, because they get past the problem of trying to generalize from randomized controlled trials to a particular individual. What *n* of 1 trials do very well is address the question, "What is best for this particular individual?" What they don't do (and what I think concerns you, David [Pierson]) is provide scientific medical knowledge in the sense that a randomized controlled trial does: a randomized controlled trial gets through the noise of individual variability to answer a question about general therapeutic value. So the 2 approaches have particular strengths. They generate very different types of medical knowledge. One could argue that in the clinical setting the *n* of 1 trial is particularly elegant because it answers the question about the individual directly, which is what we're faced with in most clinical situations, but it does not provide generalizable scientific knowledge in the same sense that a randomized controlled trial does.

**Guyatt:** I guess I'd say be careful about that. First, my interpretation of Dr Pierson's point was that it was not about the issue of generalizability but about the issue of substitution of physiologic end points for patient-important end points. I see Dr Pierson nodding that that's correct. The other point is illustrated by a story. We submitted a grant for 40 *n* of 1 trials, in which we would get more data per patient and then we could aggregate and say "How does the drug affect those 40 people?" The criticism was that these only applied to individual patients.

In contrast, I know grants (that were funded) of the same sample size of 40, but that collected less information per patient. In fact, our 40 *n* of 1 trials would provide a lot more information than a conventional randomized controlled trial of 40 people. So the *n* of 1 trials give information about an individual, but they also give an opportunity, if you do a large number of *n* of 1 trials in a group of people, to determine what's liable to happen in a larger population. They don't tell you what happens with your 41st person, but neither does a meta-analysis or anything else. So think of an *n* of 1 trial as a design that is also potentially aggregated across a group of individuals, and if so it could give you population information.

**Rubenfeld:** Just in case a lot of this discussion ends up being a "how to do it" for *n* of 1 trials, we might want to include some references in the discussion section about how to do it. The issue of *blinding* comes immediately to mind, because I can see lots of doctors out there thinking that they're doing *n* of 1 trials just by giving a trial of steroids, and I think it's important to understand the issues of control and blinding when you're using a patient-centered outcome. It just seems to me that we need to emphasize that if this becomes some sort of tutorial on how to do them.

# From Data to Evidence: Evaluative Methods in Evidence-Based Medicine

Michel D Landry PT MSc and William J Sibbald MD

Introduction
Evidence-Based Medicine
Evidence
  Levels of Evidence
Quantitative Methodologies
  Randomized Controlled Trial
  Meta-Analysis
Qualitative Methodologies
  Validity
  Methodology
  Data Collection, Analysis, and Results
  Interpretation of Results
Discussion
Summary

**The amount of published information is increasing exponentially, and recent technologic advances have created systems whereby mass distribution of this information can occur at an infinite rate. This is particularly true in the broad field of medicine, as the absolute volume of data available to the practicing clinician is creating new challenges in the management of relevant information flow. Evidence-based medicine (EBM) is an information management and learning strategy that seeks to integrate clinical expertise with the best evidence available in order to make effective clinical decisions that will ultimately improve patient care. The systematic approach underlying EBM encourages the clinician to formulate specific and relevant questions, which are answered in an iterative manner through accessing the best available published evidence. The arguments against EBM stem from the idea that there are inherent weaknesses in research methodologies and that emphasis placed on published research may ignore clinical skills and individual patient needs. Despite these arguments, EBM is gaining momentum and is consistently used as a method of learning and improving health care delivery. However, if EBM is to be effective, the clinician needs to have a critical understanding of research methodology in order to judge the value and level of a particular data source. Without critical analysis of research methodology, there is an inherent risk of drawing incorrect conclusions that may affect clinical decision-making. Currently, there is a trend toward using secondary pre-appraised data rather than primary sources as best evidence. We review the qualitative and quantitative methodology commonly used in EBM and argue that it is necessary for the clinician to preferentially use primary rather than secondary sources in making clinically relevant decisions.** *Key words: evidence-based medicine, qualitative methods, quantitative methods, levels of evidence, evidence-based decision-making.* [Respir Care 2001;46(11):1226–1235]

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This paper was prepared by Dr Sibbald for the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20–22, 2001, Banff, Alberta, Canada. On short notice and unavoidably, Dr Sibbald was unable to attend the conference. Thus, although the present article appears in the order of presentations at the conference, it is not accompanied by a discussion section.

## Introduction

In Thomas Homer-Dixon's *The Ingenuity Gap,* he states that society is exposed to an almost insurmountable amount of information.[1] He argues that within the past 25 years the number of published documents has doubled and that recent technologic advances such as the Internet have created a system whereby the distribution of these data are occurring at an infinite rate. The combination of increased availability of information with improved channels of information distribution is causing what he has termed "The Ingenuity Gap." Within this predicament, innovative methods are needed to more effectively manage information flow.

The situation that Homer-Dixon describes is occurring everywhere, including in organized medicine. In 1997, O'Rourke stated that a clinician would need to read 19 articles daily to remain up to date in general medicine.[2] Four years later we can only speculate as to new knowledge the average practitioner cannot access because of lack of time. Implementing strategies to address the increase in information flow is an important challenge for the clinician.[3] It is also believed that enhancing clinicians' ability to manage and evaluate research data will lead to less information overload and less delay in implementing research findings into clinical practice. Such concepts were one of the drivers for the development of evidence-based medicine's theoretical framework.

Originally, evidence-based medicine (EBM) was intended to be a systematic process whereby a clinician would effectively find and implement the "best evidence" to answer specific clinical questions. Since its inception, the growth of the EBM paradigm has been extensive, far-reaching, and has given birth to many new "spin-offs," such as evidence-based health care,[4] evidence-based dentistry,[5] and even evidence-based librarianship.[6] All share a common goal; namely, to integrate the best available evidence and thereby improve overall health system efficiencies. At the same time, the growth of the EBM concept has led to a view that the expansion of EBM has distracted from its original purpose. One argument is that EBM is no longer a pure science to be used at the patient's bedside, but rather has become a "catch phrase" and that that has diluted its underlying premise. EBM has become more of an information management system, compared to its initial construct as a method to formulate principles that enable clinicians to preferentially select information most appropriate to a particular clinical situation.

Clearly, growth of the EBM paradigm has been successful, and it is widely used in both clinical practice and research. A current challenge is to continue to develop EBM so that information overload is managed effectively for clinical practice and patient care to benefit from new science in a timely manner. In order for the EBM process to be effective, however, the individual clinician needs to develop a certain set of skills, such as critical appraisal of evidence. It is in this context that we will discuss (1) critical appraisals of quantitative and qualitative research methods in EBM and (2) some of the current use trends in EBM. By understanding these concepts the clinician will be able to integrate and improve patient care through diligent use of best evidence. We will also attempt to place EBM into the evolving health care environment.

## Evidence-Based Medicine

The "old" practice of reflecting on clinical experience and then seeking advice from local experts or a textbook was termed "authority-based" medicine by Chalmers.[7] EBM has promoted advances in regard to underlying methodologies used by health care practitioners to answer important clinical questions. Investigators at McMaster University (Hamilton, Ontario) were some of the first to propose a systematic methodology to integrate "evidence" with clinical practice. This approach was originally intended as an undergraduate teaching method. Over time, however, EBM was increasingly adopted by medical practitioners in the clinical environment. The value of the discipline has led to EBM being included in many—probably all—undergraduate, postgraduate, and continuing medical education programs.[8]

The most frequently used definition of EBM is ". . . the conscientious, explicit, and judicious use of current best evidence in making decisions about care of the individual patients."[9] The EBM approach requires initially that clinicians convert their information needs into a structured question and then conduct an efficient search for relevant literature to address the question. This method empowers the clinician to independently locate evidence and critically appraise it for validity and generalizability, and to integrate best evidence with patient care. This evaluation is somewhat iterative and proposes that clinical decisions be based on evidence from population, patient, and laboratory studies, rather than on popular opinion alone.[8] Table 1 describes the 5 core steps in the process of applying EBM to a specific question.

Despite a solid foundation in educational theory and clinical practice, the effectiveness of the EBM process remains controversial to some. Kerridge et al have argued that valid and reliable research-based evidence does not necessarily translate into better decision-making.[11] Their rationale is that EBM offers a strategy for improved medical practice, but the methods behind actual decision-making are not clear. It is also argued that there are inherent

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Table 1. The 5 Steps Involved in Evidence-Based Medicine

| Step | Description |
|---|---|
| 1 | Develop a clinical question that is specific. |
| 2 | Collect the best evidence that will answer the question. |
| 3 | Critically appraise the evidence for validity and applicability. |
| 4 | Integrate the critically appraised information with clinical expertise and patient-specific needs, values, and circumstances. |
| 5 | Evaluate the effectiveness and efficiency of the first 4 steps, then determine how to improve them. |

[1] Adapted from Reference 10.1

weaknesses in the randomized controlled trial (RCT) approach to testing efficacy (the gold standard of EBM evaluation). Despite these arguments, many health professionals currently use the EBM approach as a method to improve patient care. An example of the growth of the EBM approach in clinical medicine is the increasing number of EBM reports in the literature. A search in MEDLINE using the term "evidence-based medicine" and "evidence-based health care" reveals that between the years 1987 and 1992, there was only 1 EBM reference cited; between the years 1993 and 1996 there are 299 references listed; and between 1997 and February 2001 there are 4,498 listed references. Table 2 shows details regarding the rapid spread of EBM.

## Evidence

A basic skill clinicians need to use EBM is the ability to critically appraise the literature to determine which evidence should be considered as "best evidence." Closs and Cheater defined best evidence as "a quality research . . . [that is a] testimonial of facts tending to prove or disprove conclusions."[12] Geyman et al stated that the word "information" should be considered as "news," but that *evidence* should be considered as something "that tends to prove or provide grounds for holding a certain belief."[13] Furthermore, they reflected that this important distinction between information and evidence is often lost. The opportunity cost in using published reports is that there are large differences in both quality and appropriateness.[14] Because of that variability, published studies are initially categorized into primary and secondary levels. *Primary* evidence indicates original articles, such as the RCT and meta-analysis. *Secondary* evidence is generated from other sources, such as editorials, expert opinion, and practice guidelines.[13] In order to judge the value of either primary or secondary evidence, the clinician must learn analytical skills or have a practical and working knowledge related to the various research designs. Understanding the strengths and weaknesses of the various research methodologies is essential if the clinician is to adequately weigh the overall clinical value of the available evidence. The Evidence-Based Medicine Working Group has published over the past decade a series of publications entitled "The Users' Guides to the Medical Literature." Now including 36 publications, this series aims to provide a systematic approach to the appraisal of various types of published medical reports in order to determine their level of evidence and applicability to clinical practice. That series allows the clinician to quickly appraise a study based on peer-accepted evaluative criteria. The results of the series are widely referenced in the peer-reviewed literature and have been used as an evaluative framework by many investigators.[15] Table 3 summarizes the publications in the "Users' Guides to the Medical Literature" series, all of which are of tremendous value for the clinician who requires a structured approach to determining the "best available evidence" for his patient, practice, or health system.

Table 2. The Increased Publication of Evidence-Based Medicine in Peer-Reviewed Literature*

| Year(s) | EBM | EBHC |
|---|---|---|
| 1997–Feb 2001 | 4,498 | 36 |
| 1993–1996 | 299 | 10 |
| 1987–1992 | 1 | 0 |

*Results of a MEDLINE search using "evidence-based medicine" (EBM) and "evidence-based health care" (EBHC) as key words.

### Levels of Evidence

"Levels of evidence" is a hierarchical method that has been proposed to evaluate the strength of research or evidence. In this process, a designated level is applied to a publication, depending on the study methodology. There are (at least) 3 fundamentally similar methods of categorizing the level of evidence, differing only in nomenclature used to distinguish levels.

First, the United States Preventive Services Task Force grades the levels of evidence: Level I is the strongest and Level III is the weakest.[16] Level I refers to evidence that is supported by at least one randomized controlled trial. It is important to note that Level II is divided into 2 sub-levels. Level II-2 requires that evidence be obtained from a well-designed controlled trial without randomization, whereas Level II-3 requires that evidence be obtained from well-designed cohort or case-controlled studies from different research groups. Level III requires that evidence be obtained from time series with or without the intervention, uncontrolled experiments, opinions of respected authorities, and reports of expert committees.

Table 3. Topics and Publications of the Evidence-Based Medicine Working Group

| Number in Series | Year | Topic | Reference |
|---|---|---|---|
| | 1993 | Introduction and principles of the "Users' Guide" series | Guyatt GH, Rennie D. Users' guides to the medical literature. JAMA 1993;270(17):2096–2097. |
| I | 1993 | Introduction and principles of evidence-based medicine | Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA 1993;270(17):2093–2095. |
| II a | 1993 | Prevention and validity | Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1993;270(21):2598–2601. |
| II b | 1994 | Prevention and the applicability of the results | Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994;271(1):59–63. |
| III a | 1994 | Diagnostics and validity | Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1994;271(5):389–391. |
| III b | 1994 | Diagnostics and the applicability of the results | Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271(9):703–707. |
| IV | 1994 | Harm | Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA 1994;271(20):1615–1619. |
| V | 1994 | Prognosis | Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994;272(3):234–237. |
| VI | 1994 | Overview | Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA 1994;272(17):1367–1371. |
| VII a | 1995 | Clinical decision-making and validity | Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1995;273(16):1292–1295. |
| VII b | 1995 | Clinical decision-making and applicability of results | Richardson WS, Detsky AS. Users' guides to the medical literature. VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? Evidence Based Medicine Working Group. JAMA 1995; 273(20):1610–1613. |
| VIII a | 1995 | Practice guidelines and validity | Hayward RS, Wilson MC, Tunis SR, Bass EB, Guyatt G. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA 1995;274(7):570–574. |
| VIII b | 1995 | Practice guidelines and applicability of results | Wilson MC, Hayward RS, Tunis SR, Bass EB, Guyatt G. Users' guides to the Medical Literature. VIII. How to use clinical practice guidelines. B. What are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. JAMA 1995;274(20):1630–1632. |
| IX | 1995 | Recommendations | Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274(22):1800–1804. |
| X | 1996 | Variation in outcomes of health services | Naylor CD, Guyatt GH. Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. The Evidence-Based Medicine Working Group. JAMA 1996;275(7):554–558. |
| XI | 1996 | Clinical utilization review | Naylor CD, Guyatt GH. Users' guides to the medical literature. XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. JAMA 1996;275(18):1435–1439. |
| XII | 1997 | Health-related quality of life | Guyatt GH, Naylor CD, Juniper E, Heyland DK, Jaeschke R, Cook DJ. Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. JAMA 1997;277(15):1232–1237. |

(*Table continues*)

Table 3. Continued

| Number in Series | Year | Topic | Reference |
|---|---|---|---|
| XIII a | 1997 | Economic analysis and validity | Drummond MF, Richardson WS, O'Brien BJ, Levine M, Heyland D. Users' guide to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1997;277(19):1552–1557. |
| XIII b | 1997 | Economic evaluation and applicability of the results | O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1997; 277(22):1802–1806. |
| XIV | 1998 | Clinical trials | Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA 1998;279(7): 545–549. |
| XV | 1999 | Disease probability for differential diagnosis | Richardson WS, Wilson MC, Guyatt GH, Cook DJ, Nishikawa J. Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA 1999; 281(13):1214–1219. |
| XVI | 1999 | Treatment recommendations | Guyatt GH, Sinclair J, Cook DJ, Glasziou P. Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA 1999;281(19):1836–1843. |
| XVII | 1999 | Recommendations for screening | Barratt A, Irwig L, Glasziou P, Cumming RG, Raffle A, Hicks N, et al. Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA 1999;281(21):2029–2034. |
| XVIII | 1999 | Clinical impact of computer-based decision-making | Randolph AG, Haynes RB, Wyatt JC, Cook DJ, Guyatt GH. Users' Guides to the Medical Literature: XVIII. How to use an article evaluating the clinical impact of a computer-based clinical decision support system. JAMA 1999;282(1):67–74. |
| XIX a | 1999 | Effect of intervention on surrogate end points | Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA 1999;282(8):771–778. |
| XIX b | 1999 | Clinical trials | McAlister FA, Laupacis A, Wells GA, Sackett DL. Users' Guides to the Medical Literature: XIX. Applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class. JAMA 1999;282(14):1371–1377. |
| XX | 2000 | Integrating evidence with patient care | McAlister FA, Straus SE, Guyatt GH, Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group. JAMA 2000;283(21):2829–2836. |
| XXI | 2000 | Electronic health information | Hunt DL, Jaeschke R, McKibbon KA. Users' guides to the medical literature: XXI. Using electronic health information resources in evidence-based practice. Evidence-Based Medicine Working Group. JAMA 2000;283(14):1875–9. |
| XXII | 2000 | Clinical decision rules | McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: How to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284(1):79–84. |
| XXIII a | 2000 | Qualitative research and validity | Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 2000;284(3):357–362. |
| XXIII b | 2000 | Qualitative research and applicability | Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care. B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA 2000;284(4)478–482. |
| XXIV | 2000 | Clinical manifestations of disease | Richardson WS, Wilson MC, Williams JW Jr, Moyer VA, Naylor CD. Users' guides to the medical literature: XXIV. How to use an article on the clinical manifestations of disease. Evidence-Based Medicine Working Group. JAMA 2000;284(7):869–875. |
| XXV | 2000 | Applying "Users' Guide" to patient care | Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA 2000;284(10):1290–1296. |

Next, Gray described levels of evidence in 5 categories, in which the strongest is Level I and the weakest is Level V.[17] A Level I study has at "least one systematic review of multiple well-designed randomized controlled trials." A Level II study has "strong evidence from at least one properly designed randomized controlled trial of appropriate size." A Level III study has a "well-designed trial without randomization, single group pre-post, cohort, time series or matched case-control." A Level IV study requires evidence from well-designed nonexperimental studies from one or more investigative groups. Last, a Level V study is the weakest level of evidence and applies to a study that expresses the opinions of respected authorities based on experience, descriptive studies, or reports of expert committees. This level is also applied to publications that are descriptive in nature.

The third method of classifying evidence was proposed by Ellis, and is again based on a scale of 5 levels.[18] Level 1 refers to an "NHS (United Kingdom National Health System) Centre for Research and Dissemination or Cochrane database review (systematic review)." Level 2 is defined by a "large scale well designed primary study, RCT, and other controlled trials." Level 3 is defined as "large scale primary studies using other methodologies." Level 4 is divided into A and B, wherein Level 4A applies when the study is descriptive in nature and includes a report. The Level 4B study expresses the opinions and experience of respected authorities based on clinical experience and professional consensus.

We note that all 3 approaches have similar weighting factors, wherein the RCT is awarded a higher level of evidence than opinion leaders in the field. Additionally, both Gray and Ellis award a higher grade to the meta-analysis than does the United States Preventive Services Task Force. Ultimately, the allocation of levels of evidence facilitates the process of deriving the "best evidence" available.

With specific respect to respiratory care, Stoller reported that respiratory therapists are effective in weaning patients from mechanical ventilation and in allocating respiratory care to adult non-intensive care inpatients based on a number of primary level sources.[19] He also offered an excellent review of the role of respiratory therapists in multiple settings by evaluating the levels of evidence as proposed by the United States Preventive Services Task Force. Unfortunately, that report highlights that only low levels of evidence exist to validate the role of the respiratory therapist in activities such as performing intubation and allocating the use of blood gases. The case can therefore be made that the respiratory therapy community must continue to support research within the profession in order to develop higher level evidence that demonstrates the effectiveness of RTs in the health system. Without higher levels of evidence, the efficiency of their scope of practice may be questioned by "redesign forces in health care," based on the level of existing evidence.

There are numerous types of research methodologies. The 2 broad categories include "quantitative" and "qualitative," and Geyman et al report that those categories can also be described as experimental and observational, respectively.[13] Table 4 describes the differences between the 2 categories.

## Quantitative Methodologies

Quantitative methodologies have also been termed "empiricism," "positivism," "hypothesis testing," and "deductive research."[20] As such, this formal and structured approach requires that the researcher collect data in a very detailed way, leading to the explanation of a generalized phenomenon irrespective of time, place, or the interaction between the two. Overall, the quantitative researcher seeks to explain causal relationships between variables.

Various types of quantitative research methods are used in published literature. Therefore, it is important for the evidence-based clinician to understand the methods of evaluating the quality of this type of research. Although there are numerous quantitative methodologies, this paper will describe 2 of the more common, namely the randomized controlled trial and the meta-analysis.

### Randomized Controlled Trial

The RCT is considered the gold standard in quantitative research. This methodology is regarded so highly because of a strong experimental methodology wherein a cohort is randomly allocated to an exposure condition and/or a con-

Table 4. The Difference Between Quantitative and Qualitative Methodologies

| | Description | Examples |
|---|---|---|
| Quantitative (experimental) | An intervention is made and variables are manipulated. The methodology seeks to discuss causation. | Randomized controlled trial (RCT) |
| Qualitative (observational) | No intervention is made and the variables are not manipulated. The methodology does not attempt to discuss causation. | Cohort, case-control, cross sectional, descriptive surveys, case reports |

(Adapted from Reference 13.)

trol condition.[21] One of the important parts of this design is that each study participant has an equal chance of being allocated to the exposed group or the control group. The results of the RCT facilitate understanding of causal relationship between disease and intervention.

There are many advantages to the RCT experimental design. The randomization process provides the best chance of balancing confounding variables that are not necessarily identified by the investigator. The RCT also increases reproducibility and diminishes the chances of co-intervention and contamination of the results. The disadvantages of the RCT methodology are that it requires detailed planning and that it may be ethically difficult to randomize participants to the control group. In EBM, the RCT is among the strongest primary evidence used to affect clinical decisions.

There are some who report inherent weaknesses of the RCT. In the case of low back pain, Koes et al reported that the reproducibility of the results of RCTs is poor because of the unsatisfactory description of methods in the reports.[22] They added that thoroughness of the report's methods section was negatively associated with study outcome, meaning that studies showing a positive effect had poorer descriptions in the methods section than those that showed negative effects. This highlights the importance of evaluating the methodology of a study prior to judging it to be the best evidence.

### Meta-Analysis

Meta-analysis is a form of systematic review, with a planned method for using original studies as subjects or units of analysis. A meta-analysis is the statistical analysis of the results of 2 or more scientific studies in order to synthesize findings.[23,24] The synthesis of the original reports is done in a fashion that limits the amount of bias. The meta-analysis thus provides a framework for a systematic review that increases the statistical power of smaller, poorly powered studies by pooling available data, providing an overall point estimate and range of an effect, and finally identifying variability among the results. The steps involved in conducting a meta-analysis process are: identify the clinical question, develop a protocol, establish criteria to locate publications, filter out and select publications that are not relevant, appraise the quality of the studies, determine the heterogeneity of the data, estimate their precision, and report on the variability and biases in the results. The results of the meta-analysis are usually expressed as differences between 2 means, relative risk, odds ratio, and the number needed to treat effect.

Unfortunately, the meta-analysis has also been criticized. One problem with meta-analysis is that it does not remove subjectivity in the data synthesis process. Also, it does not identify sources of variability among trials and does not result in simple statistical results for complex clinical questions. Jadad et al compared systematic reviews and meta-analysis published by the Cochrane Collaboration with similar publications in journals listed on MEDLINE.[3] They reported that the Cochrane review appeared to have greater methodologic rigor than most published meta-analyses, and the information was more frequently updated than those published in peer-reviewed journals. Here again, it is essential that the clinician evaluate the methodology in order to judge its overall applicability to clinical practice.

### Qualitative Methodologies

Guba and Lincoln developed the naturalistic inquiry typology for the field of education, and they asserted that both qualitative and quantitative research methods can be used to investigate any research question.[25] Qualitative research may seem anecdotal within the context of organized medicine, but it has also been suggested that medicine is more than the application of scientific rules. Furthermore, Giacomini and Cook asserted that qualitative measures are as important as quantitative studies and that qualitative measures offer "insight into emotional and experimental phenomena."[26] Qualitative research methodology asks questions that are different from clinical epidemiology because it seeks to understand the broad complexity of events in a particular situation rather than answers for a specific question. Green and Britten state that qualitative research can investigate perceptions, attitudes, preferences, and ultimately determine the most applicable way to translate data to clinical practice.[14] Whereas the basic question asked by quantitative researchers is "how many" or "to what extent," the qualitative investigator essentially asks "why."

To assess the strength of qualitative research, the clinician must make clear a distinction between anecdotal personal accounts and structured research methodology. Rigorously conducted qualitative research must have explicit sampling strategies, systematic analysis of the data, and explanation of the underlying and emerging theories, while recognizing that the overall generalizability of qualitative methods may be conceptual rather than numerical. Giacomini and Cook proposed that there are 5 aspects that the evidence-based clinician must consider when evaluating qualitative research: (1) validity, (2) methodology, (3) data collection and analysis, (4) results, and (5) interpretation of the results.[26]

### Validity

Qualitative investigators prefer to focus on the "credibility" of data rather than on their validity.[27] Despite this, there continues to be a need for research designs to include

systemic observation and interpretation in order to achieve credibility. Once the clinician has judged the information credible, it is likely that it will lead toward more appropriate interpretation of results in the social context of the study. The evidence-based clinician must therefore be prepared to evaluate the relevance of the study to his or her clinical environment. Furthermore, the clinician must evaluate whether the methodology will address the research question and whether it was conducted in a rigorous and detailed manner.

### Methodology

The methods section of a qualitative study should include detailed description of the inclusion/exclusion criteria. Because of the importance placed on the context in which the qualitative study occurs, it is important that the unit of analysis included be representative of the phenomena being investigated. The units of analysis in this type of study can include individuals, groups, documents, artifacts, interactions, dialogues, incidents, or settings.[26] Ventres et al have argued that the unit of analysis should not be the participant alone, but rather it should be the multifaceted social interaction that occurs within the unit and study environment.[28]

There are a number of different quantitative research methodologies that can be used to answer a clinical question. Field observations, interviews, and the Delphi methods[29] are some of the more common qualitative methodologies found in peer-reviewed literature and will be reviewed here.

Field observations are designed to understand social phenomena.[22] They usually occur either directly by the investigators or indirectly through other means such as information transcription. In the direct observational method, the investigator becomes part of the social context of the study. In the indirect methods, the investigator records the events that are occurring or have occurred. As there is potential for biased interpretation of data in either of these situations, more than one type of data are often used to strengthen associations and reduce bias.

The interview technique is widely used in qualitative research. A semi-structured interview with an individual or focus group is used to gain an in-depth view of a question. Giacomini and Cook suggested that a more structured approach such as standardized questionnaires might not necessarily be "qualitative research" because the presumed answers by the respondent do not allow for an exploration of the social context.[26] Document analysis normally includes the review of charts, journals, correspondence, and other documents, but these techniques are most frequently used in the fields of policy and organizational structure of a particular organization.

The Delphi survey technique[29] is a very structured methodology that allows for a systematic refinement of expert opinion, with the goal of agreeing and reaching a consensus. In this methodology, "experts" systematically review past experiences and develop a new framework to further understand the important clinical questions. Benefits of this model include the use of expert opinions, systematic refinement, and development of consensus. There are, however, challenges in using this research methodology. For instance, the concept of "expert" has been questioned because, although it is a valid construct, it is difficult to accurately identify who possesses "expert" qualities. Other criticism includes the fact that the consensus resulting from the technique is often arbitrary and not defined in clear statistical terms, and there is potential for research bias at all stages of the process. Ultimately, it has been reported that the expected consensus in the Delphi survey technique is inherently optimistic and that instead of producing evidence, the Delphi methodology might produce "self-affecting prediction" that might not be applicable to clinical settings.[29]

### Data Collection, Analysis, and Results

Following the methodology, the clinician must determine if the social setting was observed in a sufficiently thorough manner. Giacomini and Cook remind us that this is not determined by the sample size; rather, it is determined by results that produce an in-depth analysis of the environment under investigation.[26] The data collected must effectively be in sufficient breadth and depth to support interpretation made from the study. Also, the data collected must be sufficient to support rich and robust descriptions of events.

The analysis of the data must organize the results into a framework that is not altered by the ongoing iterative process of data collection. In other words, the situation under investigation must be described sufficiently so that the further inclusion of units of analysis does not alter the framework that is being theorized. That point has been referred to as "theoretic saturation" or "information redundancy." In the final analysis, the multiple sources of information should be triangulated so as to allow for integration and explanation of the observational data.

### Interpretation of Results

Ultimately, just as with quantitative research, the clinician will be required to interpret the information presented and determine its value. The ultimate criterion that must be addressed is whether the study provides a useful pattern that is applicable in similar situations. Finally, the results of quantitative research are narrative and must contain a description of the theory to support and justify the out-

comes. Overall, it is important that within qualitative research, the clinician evaluate the results obtained in order to judge it to be "best evidence." Table 5 summarizes the important questions that the clinician must ask when determining if a qualitative study should be considered "best evidence."

## Discussion

Reports from academic and clinical facilities indicate that EBM is increasingly being used within all of health care's organizational and educational domains. Closs and Cheater argue that EBM is an essential tool if a clinician is to provide the most cost-effective and clinically effective care.[12] Perlstein et al provided an example of the effectiveness of the EBM approach.[30] They described a situation where the EBM approach was used to answer questions related to patients being admitted to hospital with bronchiolitis. They initially identified practice patterns that showed admissions to hospital were higher than expected, while the rationale for admittance was unclear. A research team identified this issue as a clinical concern and translated it into a question leading them to search for and identify the best evidence available, ultimately resulting in development of a practice guideline. A review of the efficiency of the guideline implementation was done (1 y follow-up) and showed that it continued to be highly effective in modifying and streamlining clinical care. In this specific case, the impact of EBM in a clinical setting revealed encouraging results.

Table 5. Important Questions That the Evidence-Based Clinician Should Ask When Evaluating Qualitative Research

1. Are the results of the study valid?
   - Were participants relevant to the research questions, and was their selection well reasoned?
   - Were the data collecting methods appropriate for the research objectives and setting?
   - Were the data collected comprehensive enough to support rich and robust descriptions of the observed events?
   - Were the data appropriately analyzed and the findings adequately corroborated?
2. What are the results of the study?
   - How evocative and thorough is the description?
   - How comprehensive and relevant are the theoretical conclusions?
     - What major and minor concepts does the theory entail and how well defined are they?
     - What are the relationships between the conceptual categories?
     - Are these dynamics clearly described and do they make sense?
     - Are the concepts adequately developed and illustrated?
     - What does the empirically generated theory confirm in relation to existing theory and beliefs in the field?
   - Is the study relevant to my environment?
3. How do the results of this study help me care for patients?
   - Does the study help me understand the context of my practice?
   - Does the study help me understand my relationship with my patients and their families?

(Adapted from Reference 26.)

In the Perlstein study, primary sources of information were used to develop the practice guidelines.[30] However, there is a current trend toward using secondary pre-appraised sources rather than primary sources of evidence.[31] One reason for this trend is the ease with which secondary evidence is available from groups such as the Cochrane Library or journals such as the *ACP Journal* and *Evidence-Based Medicine*. Furthermore, other Internet-based resources are available and provide pre-appraised secondary level information. The current use of information sources highlights a trend that may become important in the future development of EBM.

Guyatt et al recently identified another trend in EBM.[31] They noted that not every medical trainee is interested in gaining advanced skills in the necessary critical evaluation techniques required for EBM, and up to 72% of general practitioners use evidence-based summaries rather than original articles to determine best evidence.[31] Those results highlight that a high percentage of those surveyed believed that learning EBM skills was not effective in moving toward evidence-based decision-making. It seems that few clinicians have the time to search for primary evidence related to their clinical questions and thus many might not be interested in gaining those skills, because they believe that they will not have sufficient time to dedicate toward their application.

There may be another problem with using pre-appraised secondary levels of evidence. Placing emphasis on secondary sources rather than the primary sources of evidence may in fact produce evidence that is not sufficiently explicit to answer particular clinical questions. Although using secondary evidence is in the direction of EBM, it may simply not be enough to satisfy the goals of the evidence-based decision-making process. On the other hand, clinicians who develop advanced evaluation skills will be advantaged, as they can then access and determine whether secondary sources are consistent with best evidence from primary sources and will be able to use primary sources when secondary sources are not available. The argument for using primary rather than secondary evidence will be a central theme in the future of EBM. Although time constraints and the ease of access to secondary sources in clinical practice will continue to be a reality, it will be increasingly important to encourage clinicians to use both primary and secondary sources.

## Summary

EBM is a strategy that can be used by the busy clinician to manage an ever-increasing flow of research data. The

ability of clinicians to demonstrate analytical skill in EBM is of paramount importance if primary and secondary levels of published information are going to be used in an effective manner to positively affect patient care. Guyatt et al have reported that quality of care must be consistent with best evidence; thus it is important for the clinician to understand how to critically analyze both qualitative and quantitative data in order to best answer the questions that are being—or should be—asked.[31] Though Paton suggested that EBM is not a panacea for improved medical intervention,[27] herein we have argued that, rather than being a singular event, EBM is an active process for elaborating and facilitating clinical learning. In developing efficient information management strategies through EBM, the clinician will then be able to reproach Homer-Dixon's "Ingenuity Gap."

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# Assessment of Health-Related Quality of Life

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Introduction
Concepts of Health-Related Quality of Life
Important Criteria for Health-Related Quality of Life Assessment
  Psychometric Properties
  Thoughtful Administration and Use of Health-Related Quality of Life Instruments
  Diverse Population Issues
Children's Health-Related Quality of Life
  Administration of Health-Related Quality of Life Instruments to Children
Caregivers' Health-Related Quality of Life
Literature Review of Health-Related Quality of Life Instruments
  Agreeing on the Strategy for Review
  Assessing Citations for Inclusion and Writing the Manuscript
  Categories/Types of Health-Related Quality of Life Instruments
Summary

**In addition to mortality, morbidity, and patient satisfaction, health-related quality of life (HRQOL) is an outcome of health care as well as a consequence of illness or injury. Consequently, instruments to assess HRQOL have become important outcome measures for the evaluation of health care. The last 2 decades have seen the development of hundreds of HRQOL instruments, which are increasingly being incorporated in clinical trials. However, for HRQOL instruments to be valid outcome measures, a variety of factors must be addressed, including conceptual and methodological issues. In addition, there must be careful selection and thoughtful administration. The present report discusses these issues in addition to the scoring and interpretation considerations for the valid assessment of HRQOL. We provide an overview of generic, disease-specific, and utility measures. Using disease-specific instruments pertinent to respiratory care, we discuss their validity, reliability, responsiveness, and minimum clinically important difference. We conclude with recommendations regarding which HRQOL tools have documented evidence that they are psychometrically sound for application to research and clinical practice in respiratory care.** *Key words: health-related quality of life, evidence-based medicine.* [Respir Care 2001;46(11):1236–1255]

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A version of this paper was presented by Dr Mishoe during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20-22, 2001, Banff, Alberta, Canada.

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## Introduction

Health care professionals, including respiratory therapists (RTs), recognize that illness and injury can have profound effects on a person's quality of life. As early as 1947, the World Health Organization described health as a "state of complete physical, mental and social well being, and not merely the absence of disease or infirmity."[1] However, most health care services in the past focused on the treatment of pathophysiology, with less attention to the whole person, including emotional and social aspects. In today's climate of growing concern about costs of health care, professional accountability, the effectiveness and efficiency of treatment, and equity of access to care, health care outcomes and evidence-based medicine have become increasingly important.

Health-related quality of life (HRQOL) assessments are now routinely incorporated as outcome measures in randomized controlled trials to evaluate the effectiveness of health care. Much has been learned to incorporate HRQOL measures into multicenter randomized controlled trials with little missing data. Gradually, health care is shifting from a disease-oriented approach to a patient-oriented approach. RTs and all other health professionals should understand measures of HRQOL and realize their value, use, and limitations.

## Concepts of Health-Related Quality of Life

Quality of life can be defined as an individual's overall satisfaction with life and general sense of personal well being.[2] Quality of life is subjective well being—a person's satisfaction or happiness with life in the domains he or she considers important.[3] Consequently, quality of life is complex, subjective, and multidimensional, involving the importance of a domain to a person and how satisfied a person is with that domain. In other words, a person can maintain a high quality of life in spite of dissatisfaction with a particular domain if that aspect of life is relatively unimportant (or the person has adapted and learned to cope). For example, a person may have severe asthma and be restricted in the ability to play sports yet still have a high quality of life.

Numerous taxonomies have been proposed to describe quality of life, including health status, physical, mental, and material well being, relations with other people, social role, personal development, fulfillment, and recreation.[4] HRQOL encompasses the areas of physical function, somatic sensation, psychological state, and social interactions that are affected by one's health.[5] Clearly, symptoms of illness, health perceptions, and overall quality of life are often included in the overall domain of HRQOL.[6] The comprehensive dimensions of HRQOL include (1) health status/health perceptions/level of wellness or illness, (2) functional status/ability to perform daily activities and physical activity, (3) mood/emotional state and response to stressors, and (4) symptoms/perceptions of abnormal physical, cognitive, and/or emotional state.

More than 54 million Americans experience some limitation of their activities as a result of chronic health problems.[7] The Centers for Disease Control predict that the prevalence of activity limitations or disability will increase by about 50% in the United States by the year 2010 because of the demographic shift, improvements in overall survival from common illnesses, and increased life expectancy.[7] HRQOL is an outcome of health care as well as a consequence of illness or injury. Some would say that HRQOL is the most important outcome of health care and also a powerful predictor of mortality and morbidity.[8–10]

In the past 2 decades there has been an exponential increase in the study of HRQOL in clinical research, in particular in the past 5 years. For example, in 1973 only 5 articles listed "quality of life" as a reference key word in the MEDLINE database; that number grew to 16,256 in 1998, and to 128,156 in our current search. When limited to evidence-based medicine reviews, that number drops to 63, and then 14, and then 8 when limited further to asthma and chronic obstructive pulmonary disease (COPD), respectively.

## Important Criteria for Health-Related Quality of Life Assessment

Historically, acknowledgement that quality of life is a valid outcome measure has been hampered by a variety of factors, including the conceptual vagueness, assessment tools of dubious validity and reliability, the inappropriateness of methods, and the weakness of statistical analysis of the resulting data.[11] HRQOL instrument development involves selection of items that might reasonably be measured; item scaling, item reduction, assessment of internal consistency, and determination of validity, reliability, and responsiveness. Specific criteria apply to each of these aspects of development. Three additional criteria require consideration when selecting, using, interpreting, and applying HRQOL assessments. First and foremost, the instruments used must be psychometrically sound. Second, once an instrument is developed and determined to be psychometrically sound, the intended use of any HRQOL instrument is an important consideration for its valid use. That is, there must be thoughtful administration. Third, there must be correct analysis and interpretation. Table 1 lists the considerations for HRQOL assessment described herein.

### Psychometric Properties

Psychometric assessment involves developing and testing an HRQOL instrument for its validity, reliability, re-

Table 1. Considerations for HRQOL Assessment

| | |
|---|---|
| Choosing instruments | Identity of respondent (patient, caregiver, child, clinician) |
| | Setting of the evaluation |
| | Respondent and administrative burden |
| | Type of instrument used |
| | Approach to evaluation (general and/or disease-specific) |
| | Psychometric properties (validity, reliability, responsiveness, intended use) |
| | Properties of instrument under study conditions (adaptations) |
| | Coverage |
| Types of instruments | Short form (Likert-type scale, visual analog scale) |
| | Self-assessment instrument (by written form, computer, phone recording) |
| | Interview-administered form |
| | Interview (in person, by phone) |
| | Clinic-based survey |
| | Mail-back survey |
| Intended use and timing | Intended use (evaluative, discriminative, predictive) |
| | Timing |
| | Study objectives (risk to benefits and cost to benefits) |
| | Natural history of disease (seasonal differences?) |
| | Baseline measures |
| | Time since initiating therapy |
| | Number of assessments (interpretable minimum) |
| Clinical relevance | Statistical significance |
| | Clinical importance |
| | Validity under study conditions |
| Diverse population | HRQOL and effectiveness research needs to represent increasing diversity |
| | Culturally sensitive research must include cultural subgroups. |
| | Need to examine cultural equivalence of HRQOL measures. |
| Children's assessment | Administer to children separate from caregivers |
| | Parent or caregiver serving as proxy? (which parent?) |
| | Reading level appropriate or interviewer-administered |
| | Use of symbols instead of words |
| | Reasonable length/time |
| | Avoid slang/regional terms |

HRQOL = health-related quality of life

sponsiveness, and coverage. Every HRQOL instrument must establish and describe each of these psychometric properties to be useful as a tool for research, evidence-based medicine, and clinical decision-making.[5,12,13] Table 2 provides an overview of HRQOL psychometric properties for nonstatisticians. The following 7 sections elaborate these psychometric properties.

**Validity.** The validity of an instrument is defined as the degree to which it measures what it claims to measure. It is critically important to realize that validity testing is not an all-or-none approach and that calling an instrument valid is relative. The validity of a measurement instrument does not refer to the instrument itself, but to whether the interpretations of its scores are justified. Therefore it is necessary when discussing HRQOL assessment and evaluating instruments to determine what evidence exists for the validation of an instrument. Furthermore, clinical trial protocols should incorporate the rationale and instructions for HRQOL assessment, to assure validity within the research study.[8] Clinical protocols should explain why, how, and when HRQOL assessments will be completed, provide a justification for the instruments selected for use, and describe how the data will be analyzed. An overall assessment of an instrument's utility and limitations is not established once and for all; rather, it is gradually built up from cumulative evidence.

There are 3 essential ways of accumulating evidence for the validity of an instrument: content-related, construct-related, and criterion-related. Content validity evaluates whether items or groups of items adequately represent the intended domains of an instrument. A common method to obtain evidence about content validity involves the use of expert and lay panels to make judgments about the clarity, comprehensiveness, and redundancy of items and scales of an instrument. Developers of HRQOL instruments must assess whether the items included comprehensively represent the important patient concerns for a disease or group of diseases. Content validity is closely related to the intended use of an instrument and whether an instrument is designed to be evaluative, discriminative, or predictive. These concepts are elaborated further below, in the section on intended uses of HRQOL instruments.

Construct validity is probably the most difficult and perhaps most important to establish. Construct validity is established by providing evidence that a proposed interpretation of scores for an instrument is based on an established theoretical construct. A construct is a theoretically derived notion of the domains one wishes to measure. Common methods to derive construct validity include examination of the logical relations that should exist with other measures or patterns of scores across groups of individuals. For example, if a disease-specific instrument has construct validity, it should be able to discriminate

Table 2. Psychometric Properties of HRQOL Instruments for Non-Statisticians

| Required Properties | Statistical Description | "Plain English" Description or Notes |
|---|---|---|
| Content validity | Groups or items represent the intended domain | Evidence that experts agree indicate that the instrument asks questions on what it claims to measure |
| Construct validity | Proposed interpretation of scores is based on an established theoretical construct, discriminative properties | Evidence that the instrument can discriminate between persons with and without the trait (illness) |
| Criterion validity | The extent to which scores relate to an agreed criterion (a gold standard) | Not possible for HRQOL because health is subjective and there is no single gold standard |
| Reliability | The precision of an instrument or the degree to which it is free from random error | Evidence that when there is no change in the patient you achieve the same score |
| Responsiveness | The sensitivity, which is the ability of an instrument to detect change when it occurs based on longitudinal data and expressed as effect sizes | Evidence over time that the instrument can detect differences when comparing a group expected to change with a group that is not expected to change |
| Additional Properties | | |
| Minimum clinically important difference | The smallest difference that a patient can perceive in a domain that is important to the patient that would indicate a change in patient management in the absence of excessive costs or undesirable side effects | Evidence that patients and clinicians understand and agree how much change in HRQOL is important enough to change course of therapy |
| Cross-sectional validity | Relationship to disease reference measures | Evidence that when there is a change in HRQOL score there is also a change in the patient's condition (eg, $FEV_1$) |
| Longitudinal validity | Relationship over time | Evidence that the instrument's results are stable over time in the same individuals when there is no change |
| Concurrent validity | Relationship to other measures and alternative forms | Evidence that an instrument compares favorably with another (generally one that is more established) or with other supporting data |

HRQOL = health-related quality of life
$FEV_1$ = forced expiratory volume in the first second.

between persons who do not have asthma and those who have mild, moderate, or severe asthma.

Criterion-related validity shows the extent to which the scores from an HRQOL instrument relate to an agreed criterion. Criterion measures are widely accepted measures or gold standards of a particular construct. It is not possible to establish criterion validity for HRQOL instruments because of the subjective nature of the construct and therefore the lack of an accepted standard.

In addition to these forms of validity, HRQOL instruments should have documented evidence of concurrent validity, longitudinal validity, or cross-sectional validity. Concurrent validity is established by showing a relationship between an HRQOL instrument and other measures. Concurrent validity should also be established among alternative forms of any HRQOL instrument to show comparability when there is more than one version. Longitudinal validity is established by showing relationships over time, such as showing an instrument has stability over time when there is no change in patient health status. Longitudinal construct validity should be established for any evaluative HRQOL instrument. Cross-sectional validity is established by showing relationships between HRQOL measures and other disease reference measures such as blood pressure or pulmonary function test results.

**Reliability.** Reliability is the accuracy or precision of an instrument, or the degree to which the instrument is free from random error.[14] A reliable instrument achieves precision or reproducibility of the measure. Reproducibility is established by test-retest reliability. A reliable instrument should achieve stable scores among respondents over time when there is no change in the domain being assessed. For instruments administered by an interviewer, inter-observer and intra-observer reliability is needed to show agreement in measures over time and between interviewers.

Reliability also includes the internal consistency of the instrument. Internal consistency is established using Cron-

bach's alpha, which provides a coefficient estimate of reliability based on all possible correlations between 2 sets of items within an instrument.[15] When the instruments have dichotomous response choices, such as yes/no, the Kuder Richardson Formula (HR 20) is used. An HRQOL instrument should have commonly accepted minimum standards for internal consistency reliability reported as an alpha coefficient of 0.90 - 0.95 for individual comparisons and 0.7 for group comparisons.[12] A discriminative instrument should have high internal consistency, meaning the items on the instrument relate to each other and measure the same thing. It is not necessary for evaluative instruments to have high internal consisteney; rather each item must be consistent in how it measures change over time. A discriminative instrument must also have high test/retest reliability, thus minimizing noise.

**Responsiveness.** Responsiveness refers to the sensitivity of the instrument—its ability to detect change. Responsiveness is a measure of the association between changes in the scores of an instrument and the underlying changes in the clinical condition. Claims of an instrument's responsiveness should provide evidence that the measure can detect differences in outcomes, even when those differences are small. For any claim that an instrument is responsive, evidence should be provided on the change of scores, ideally expressed as effect sizes. Claims for an instrument's responsiveness should be made by comparing a group that is expected to change with a group that is not expected to change, derived from longitudinal data. Responsiveness can be represented by the magnitude of the change in scores associated with a given change in HRQOL. Usually, disease-specific HRQOL instruments are more responsive than generic instruments.

**Coverage.** The choice of HRQOL instruments should be based on the study population, patient disease(s), researcher preference, and specific aims or intent for assessment of HRQOL. Most studies incorporate a combination of generic and disease-specific instruments to enhance coverage. Both sensitivity and generalizability can be achieved when a combination of various types of HRQOL instruments is used.[16] Generic instruments help achieve generalizability because of their applicability to large samples with a variety of diseases. They are ideal to assess conditions of comorbidity and to make comparisons across groups with different diseases. Disease-specific instruments are sensitive to small changes in HRQOL, making them ideal for evaluative and discriminative purposes. Utilities are used to determine what aspects of health the patient values the most, facilitating decision-making by patients and providers, balancing costs with benefits, as well as risks and benefits. With careful selection and administration of generic, disease-specific, and utility measures, broad coverage is possible without a drastic increase in administration time or burden.

### Thoughtful Administration and Use of Health-Related Quality of Life Instruments

Once the psychometric properties of instruments are determined, the valid assessment of HRQOL requires careful and considerate administration. The validity of any HRQOL instrument is jeopardized if the instrument is used in any way other than originally intended. Therefore, additional validity evidence is needed whenever an HRQOL instrument is modified from its original intention. No change should be made to an HRQOL instrument without permission from the developer(s).[17]

The timing of the HRQOL assessment in the course of a clinical trial depends on the purpose (eg, determining whether treatment is having an impact on disease-related HRQOL or whether a particular medication such as theophylline is having a toxic effect). All patients who consent to participation in a clinical trial should have a baseline assessment before randomization or treatment begins.[18] The baseline assessments of HRQOL allow comparison of groups for balance of HRQOL characteristics as well as valid assessment of HRQOL before any knowledge of group assignment. Clinical trial protocols should incorporate the rationale and instructions for HRQOL assessment. More recently there has been a move toward specifying in a trial the exact HRQOL hypothesis and how results will be interpreted.

**Intended Use: Evaluative, Discriminative, Predictive Purposes.** As HRQOL instruments differ in their measurement properties, this influences how an instrument ought to be used. A methodological framework for HRQOL instruments has been proposed, since the required psychometric properties differ according to the intended purpose, which can be classified as evaluative, discriminative, or predictive.[13,19] Thus, when selecting an HRQOL instrument, a clinician or researcher must consider why each instrument under consideration was developed, because there are no specific criteria indicating what aspects of a person's life should be included in HRQOL assessment.[20] For any of these instruments, the items do not have to be comprehensive. Rather, the items must sample areas related to change in health status (evaluative), differences between healthy and unhealthy persons (discriminative), and determination of disease severity (predictive).

Evaluative instruments are used to quantify the benefit of a treatment during a clinical trial or clinical practice. Evaluative instruments are also used to assess the benefit of a community intervention. Thus, evaluative tools should have the potential to capture a change in a patient's condition associated with an intervention. Items on an evalu-

ative instrument must be consistent in how they measure change over time. When a patient is clinically stable, scores on an evaluative HRQOL instrument should not significantly differ between 2 points in time. The measurement properties required for evaluative instruments are responsiveness and longitudinal validity.[19]

A discriminative instrument distinguishes among individuals or groups on the basis of some underlying dimension at one point in time. Items for a discriminative HRQOL instrument should reflect features of daily living that are substantially affected by disability related to the disease of interest. The items should be important to patients with that disease and stable over time. For example, with an asthma-specific instrument, discriminative items might include school attendance and ability to participate in sports or other physical activities such as running. The measurement properties required for good discrimination are reliability and cross-sectional construct validity.[19]

A predictive instrument is used to classify individuals into a set of predefined categories, either concurrently or prospectively, when a gold standard is available. For a predictive HRQOL instrument, the items should be able to project an associated criterion measure of the disease. For example, decreased expiratory flow rate (measured as forced expiratory volume in the first second [$FEV_1$]) can be used as the criterion for classifying asthma patients. Any variable that predicts the airway reactivity of a patient can be used as an item in an asthma-specific predictive instrument. Examples include nighttime awakenings, coughing, shortness of breath, and wheezing, which are associated with the criterion measure ($FEV_1$). A valid predictive HRQOL instrument should classify individuals into the same category across multiple points in time.

**Burden.** Respondent burden refers to the time, energy, and any other demands placed on those to whom the instrument is administered. Evidence should be provided that an instrument places no undue physical or emotional strain on the respondent. The developers of an instrument should indicate any circumstances when their instrument is not applicable or appropriate. The amount of time it takes to complete an HRQOL instrument is generally related to the number of items, which should be reduced as much as possible to decrease the amount of time it takes to complete the questionnaire without jeopardizing the intended use or psychometric properties. Increasingly there are HRQOL instruments that are short in length, taking only a few minutes to complete, that are useful and valid for a variety of purposes when used as intended. An HRQOL instrument should provide information on the average and range of time needed for all population groups for which it is intended.

Administrative burden refers to the amount of time it takes to administer the HRQOL instrument. In addition, administrative burden relates to the amount of time it takes to score and interpret data gathered from the instrument. Information should be provided about the average time and range of time required for a trained interviewer to administer the instrument. Also, if specific resources such as computers are required for administration, scoring, or analysis, that should be specified. An ideal time for administration of HRQOL assessments is during the wait time for office or clinic visits. Follow-up telephone calls and mailed surveys can be useful and efficient. There are a number of short, well designed, psychometrically sound instruments that have greatly reduced respondent and administrative burden, which has facilitated HRQOL assessment for research and clinical practice.[21] Later sections herein elaborate the specific instruments for use in respiratory care.

Information on the patient's reading level should be provided, which is especially important for children's HRQOL. Whether the instrument can be self-administered or must be interviewer-administered should also be provided for all population groups for which the instrument is intended. Any special requirements or requests that may be placed on respondents, such as the need to have access to other medical data, should also be reported. Ideally there should be information provided on the special considerations for interviewer-administration of any instrument to respondents who are illiterate or have low literacy.

**Correct Analysis and Interpretation.** HRQOL assessment has steadily gained prominence in health care research and practice, bringing numerous issues to the forefront.[22] For example, it is critically important for both research and clinical purposes to demonstrate the validity of the HRQOL instruments intended for use in a study. You may recall from previous sections that validity is relative; therefore, clinical trial protocols should incorporate the rationale and instructions for HRQOL assessment to assure validity within the research study.[8,20] Clinical protocols should explain why, how, and when HRQOL assessments will be completed, provide a justification for the instruments selected for use and describe how the data will be analyzed.

Another important consideration in the validation studies of HRQOL instruments is to establish a priori predictions to minimize the risk of inappropriately rationalizing unexpected findings after the analysis.[23] With the absence of an accepted standard for HRQOL, construct validity can be established by showing correlations between the questionnaire and other related outcomes. For example, developers of the Asthma Quality of Life Questionnaire (AQLQ) made a priori predictions about the correlations they would find (weak, moderate, strong) between the 4 domains of the questionnaire and other outcomes (air flow limitation, generic quality of life).[23]

In addition, clinical protocols should explain how statistically significant findings will be used to further assess the practical or clinical importance of changes in HRQOL scores. Following the thoughtful selection for the intended use of an instrument, it is important to correctly analyze and interpret the HRQOL data. As with other outcome measures, statistical significance does not necessarily equate with clinical importance. Statistical significance is determined by many factors, including sample size, power, and the properties of the HRQOL instrument, in addition to the careful selection and use of instruments.

**Clinical Importance.** Clinicians are generally able to make meaningful interpretations of clinical data, using a wide variety of physiologic measures. For example, a 10 mm Hg change in diastolic blood pressure or a 0.5 L change in $FEV_1$ has clinical importance. However, the clinical importance of changes in HRQOL measures is more elusive because there are no standardized units for the measurement and health professionals have less experience using HRQOL data.

Determining clinically important change, which recognizes the patient's perception as well as the clinical aspects of case management and outcomes, can only be done by health care professionals who have extensive experience with the assessment instrument, the patient population, and the individual patients.[24,25] Furthermore, the relevance of change in scores depends on the perspective of the user of the information. For example, small numerical changes affecting large populations may be of interest to policymakers or epidemiologists, but clinicians may require larger changes in an individual patient's HRQOL before considering cessation of or alterations in treatment. One way to handle this dilemma is to assess the amount of change that is important and perceptible to the patient.

The most common approach to describing clinical importance is the use of the minimum clinically important difference (MCID). In addition to knowing the sensitivity of an instrument, it is useful to know how much change is important. The MCID is the smallest difference that patients can perceive and that clinicians would care about.[26,27] The MCID represents the smallest change in HRQOL in a domain that is important to a patient that would indicate a change in patient management in the absence of excessive costs or adverse effects.

It is possible to determine the MCID for disease-specific instruments, especially for evaluative instruments. For example, researchers have determined that a within-subject change of 0.5 on the AQLQ represents the minimum important change, as compared to other evaluative criteria.[27] Furthermore, the MCID for the AQLQ and its interpretations apply to the instrument as a whole, to the individual domains, and to patients who improve and those who deteriorate. Although there are no established MCIDs for the most common generic instrument, the Medical Outcomes Study Short Form 36 (more commonly known as SF-36), recent investigations into the clinical interpretation of these scales using item-response theory offer promise for the clinical interpretation of individual scores.[28,29]

Recently, researchers compared the MCID to the standard error of measurement to evaluate intra-individual change on both generic and disease-specific measures.[30,31] Findings from longitudinal studies show that a change equivalent to one standard error of measurement approximated the MCID for each domain of the Chronic Heart Disease Questionnaire[31] and the Chronic Respiratory Disease Questionnaire (CRQ).[30] It is usually not possible to derive the MCID for general measures because of the intent and nature of generic instruments. However, the one standard error of measurement criterion showed promise (in those scales with acceptable reliability and variability) when applied to the SF-36 change scores for the same outpatients, by reflecting similar percentages of individuals who improved, declined, or remained stable.[30,31] Further usefulness of the one standard error of measurement criterion could be established through additional research of those HRQOL instruments with established MCIDs. Having a numerical value such as the MCID or the one standard error of measurement criterion that appears to classify patients into various groups who are either experiencing improvement or deterioration in HRQOL can provide valuable information to health care professionals and patients.[32]

**Personality, Depression, and Health-Related Quality of Life.** Although HRQOL instruments are increasingly used as outcomes to inform health care decisions, the subjective nature of HRQOL cannot be overlooked. Some individuals see themselves as healthy despite having serious chronic illness, whereas others view themselves as unhealthy when there is no objective medical evidence of that. Although personality is known to influence patients' ratings of their own health, its effects on measurement of HRQOL are poorly understood. One study provides evidence (albeit weak, Level III evidence) that negative affectivity (a general disposition to experience negative mood states) was negatively associated with HRQOL measured by the SF-36, controlling for age and common physical and mental diseases.[33] The study showed that negative affectivity explained as much as 13.9% of the variance in HRQOL measured by SF-36.

Another recent study described the relationships between HRQOL and psychological variables relevant to asthma, indicating a significant negative correlation with perceived vulnerability, panic-fear personality, and aspects of HRQOL in asthma.[34] Other research has provided further evidence that asthma patients with more depressive symptoms reported worse HRQOL using the AQLQ than asthma

patients with similar disease but fewer depressive symptoms.[35,36] Another report found that 90% of COPD patients suffered from anxiety or depression as measured by the Hospital Anxiety and Depression Scale, compared to 52% of patients with inoperable lung cancer.[37] Thus clinicians and researchers who rely on HRQOL measures should consider that personality as well as depression can affect the subjective rating of HRQOL. Further research is needed to establish the relationships between personality characteristics and HRQOL measures. This type of research can facilitate HRQOL research and the use of HRQOL measures as an outcome to assess the effectiveness of health care.

### Diverse Population Issues

The majority of HRQOL instruments have been developed among nonminority, well-educated people. Health effectiveness and HRQOL research needs to represent the increasing diversity of cultures in the United States and throughout the world. Demographic projections for the United States population indicate that the number of Latinos, African Americans, Asians, and Pacific Islanders will grow so that, when Alaska Natives and American Indians are included, non-Caucasians will make up about half of the population by 2050.[38,39] Culturally sensitive research must include cultural subgroups, and there is a growing need to examine cultural equivalence of HRQOL measures.[40] Investigating group differences in perceptions and descriptions of HRQOL for various cultures requires consideration of the economic, cultural, and social contexts that shape those perceptions.

The most relevant diverse populations in studies of HRQOL outcomes for medical effectiveness are groups at risk for poor outcomes—so called vulnerable populations, which include women, children, the elderly, ethnic people of color, persons of low socioeconomic status, immigrants, homosexuals, and the homeless.[40,41] Other groups that have been largely overlooked in HRQOL research are the cognitively impaired, the mentally and physically disabled,[42,43] those with limited English language skills, persons of low literacy,[44] and rural populations.[45] Translation of instruments to other languages and special consideration to capture important issues and meaning for various cultural groups are increasingly important to HRQOL research. Readers should refer to the detailed papers by Mueller et al[45] and Guillemin et al[46] if performing HRQOL assessment in culturally diverse groups, to determine cross-cultural adaptation of terminology to achieve equivalence of concepts, constructs, items, semantics, operations, psychometrics, and criterion measures.

**Translation of an Instrument to Other Languages.** For translated instruments, information should be provided on how conceptual and linguistic equivalence was achieved. There are several approaches to translation of an HRQOL instrument to other languages, including single translation, double-back translation, and translation by committee. Generally, a single translation is insufficient because it will probably miss the implied meaning, capturing only the literal meaning.[40,47] It is commonly recommended that there should be at least 2 forward translations from the source language, preferably by those experienced in translation in health status research, resulting in a pooled forward translation. Then there should be at least one, preferably more, backward translations to the source language that result in another pooled translation. Lay and expert panels should review this translation to provide revisions, and a pilot study should be conducted to provide evidence of the comparability.[11]

### Children's Health-Related Quality of Life

A chronic illness such as asthma can produce considerable stress in children, which can affect physical and emotional health, school achievement, and social activities. Consequently, it is important to determine children's HRQOL. Chronic diseases affect children with various impacts on the child and his or her caregivers. For example, it is known that the potential for an asthma attack and the care required in day-to-day living can greatly affect the quality of life of the patient and the family.[48–51] Difficulty in breathing can arouse the fear of death in all individuals, and in the child it may promote a sense of inferiority and helplessness, which can influence the development of independence.[12,48,52,53] In addition, asthmatic children may feel isolated from their peers, leading to frustration, anger, and sadness.[48,54–60] A child's perception of illness can be quite different from the actual condition, thus it would be of substantial value to understand the child's perceptions and to individualize care accordingly.[54,61]

Several reviews note the scarcity of instruments to assess HRQOL in children and the numerous methodological and practical considerations for the development of adequate instruments for research and clinical purposes.[62–64] There are several disease-specific HRQOL instruments developed to measure children's perceptions of how asthma affects their quality of life, and this disease has received the greatest attention by HRQOL researchers.[48,55–58,65,66] The Pediatric Quality of Life Questionnaire,[48] the Life Activities Questionnaire for Childhood Asthma,[57] the Childhood Asthma Questionnaire (CAQ),[55] and the How Are You?[66] have validation studies with documented evidence of validity, reliability, and responsiveness for use in clinical trials. In addition, there are disease-specific instruments that have evidence of validity, reliability, and responsiveness in measuring HRQOL in children with cancer,[67] as well as generic instruments such as the German

KINDL[68] and the Child Health and Illness Profile, Adolescent Edition.[62–64]

Distress experienced by a child with a chronic illness and its effects on HRQOL may not be adequately assessed by an adult.[54,65–76] Therefore, quality of life issues should be addressed separately for adults and children.[55,73] Child-centered approaches are indicated for development of disease-specific instruments to measure the impact of chronic disease such as asthma on quality of life as perceived by children and adolescents.[54,74–76] Understanding the child's perceptions of his or her HRQOL by using disease-specific instruments designed for children can enable development of care plans designed specifically to meet the child's needs. Further evidence is needed to determine how child-centered approaches to HRQOL can improve health care outcomes.

### Administration of Health-Related Quality of Life Instruments to Children

When administering HRQOL instruments to children there are several important considerations. HRQOL instruments for children should be administered to children separate from caregivers, to minimize bias and unwanted parental influence.[55,75] However, there are no patient-completed asthma-specific instruments that have been fully validated in children under age 7. It is still controversial whether a caregiver proxy can be used to assess HRQOL in children.[50] Guyatt et al concluded that in children younger than 11, clinicians can gain valuable information from questioning both children and parents, whereas for children over 11 the parents provide little additional information.[77]

Each HRQOL instrument must be culturally sensitive and age specific. Slang and regional or local terms must be avoided to enhance validity. The considerations for diverse populations are equally important for assessment and administration of HRQOL instruments to children. The reading level must be appropriate for each child for valid assessment. In many cases the use of symbols instead of words is preferred.[56] In addition, visual analog scales, where the patient responds to a question by making a choice along a continuum, have been effective.[78,79] Whenever there is doubt regarding the reading comprehension of a child or an adult, the HRQOL instrument should be interviewer-administered. The instructions for and validity of interviewer-administered forms should be determined prior to the study.

For children as well as adults, the instrument should be reasonable in length and time for completion. Generally, the shortest possible instrument is desired without sacrificing validity, reliability, or responsiveness. Instruments having greater numbers of responses (eg, 7 choices or a continuous scale such as a visual analog scale) can achieve increased reliability and validity without requiring additional items. Furthermore, visual analog scales or use of 7-item response scales allows detection of fine gradations of change, thus increasing responsiveness, which is crucial for evaluative HRQOL instruments.[78–80]

### Caregivers' Health-Related Quality of Life

It is beyond the scope of this paper to discuss the various aspects of caregivers' HRQOL when a family member has a chronic illness such as asthma, cystic fibrosis, or acquired immune deficiency syndrome. However, it is known that caring for family members who have disease can have profound effects on caregivers' quality of life.[49,60,79] In addition, there is evidence that the quality of life of the caregiver can differ greatly from the quality of life of the person who is ill.[50,75,77]

## Literature Review of Health-Related Quality of Life Instruments

The method we used to undertake the literature review was adapted from the Cochrane Collaboration Handbook.[81] The literature review was not a formal, multi-year, externally funded, systematic review incorporating meta-analysis techniques. Instead, the requirements were simply to update RTs and other health care professionals on the existing knowledge and available evidence regarding HRQOL. In addition, our intent is to provide clinicians, particularly RTs, with the information they need to make informed choices when incorporating HRQOL instruments into their research and clinical practice. The review of the literature incorporated the following steps: agreeing on the strategy for review, developing the protocol, assessing citations for inclusion, and writing the report.

### Agreeing on the Strategy for Review

Our strategy for review was to identify the most appropriate generic, disease-specific, and utility measures for assessment of HRQOL with implications for respiratory therapy. Throughout the writing process, the authors met to review progress. In addition to formal research education, the authors have had formal training and experience in searching electronic databases such as MEDLINE and consulted with medical librarians—an invaluable source of assistance.

Specific search terms to be used in the review were developed through a process of initial reading, past experience with literature searching, and iterative learning during the review process. The linguistic and temporal framework we used to identify HRQOL instruments for use in respiratory care was as follows:

1. Review only reports written in English, except for the portion of this report describing diverse population issues.
2. Review only papers published since 1995, except for key resources already in our files describing foundational work for particular HRQOL instruments.
3. Limit our review of disease-specific instruments to asthma, COPD, and sleep-disordered breathing.
4. Focus the review of generic and utility measures to the most common instruments with documented validity for use with patients suffering respiratory disease.
5. Concentrate on the content of electronic databases, with expansion into Internet- and paper-based resources as necessary.

### Assessing Citations for Inclusion and Writing the Manuscript

Assessing the quality of papers and reports was challenging. The review focused on papers that reported the psychometric properties and other criteria specified herein and condensed in Tables 1 and 2. It was necessary to review a large number of citations to ensure that as many relevant papers as possible were identified and included. Similarly, it was necessary to retrieve and review full-text reports. Given the large number of resources available via MEDLINE and HealthSTAR, our review strictly adhered to relevant articles that met the review criteria. Interpretation of those reports and preparation of the present report were undertaken solely by the authors, which presented a substantial limitation to the comprehensiveness and rigor of the review. It is important to recognize that this process is open to criticisms of bias and that unaffiliated reviewers can be used to reduce the bias. In defense of both approaches, reviews of the same topic often disagree, and neither the expertise of the reviewer nor peer review can guarantee the validity of a review.[82] In some cases, we refer readers to other critical reviews of the topic or cite pertinent reviews to increase the comprehensiveness and usefulness of this report for clinicians. When choosing HRQOL instruments, we suggest that clinical and research teams consider this review and also conduct their own systematic review of the literature to meet the specific aims of their study.

### Categories of Health-Related Quality of Life Instruments

There are essentially 3 categories of HRQOL instrument: generic, disease-specific, and utility measures. Some distill the categorization to only 2 realms, considering utility-based instruments as a component of generic instruments.[83–84] Generic instruments are designed to incorporate multiple dimensions of HRQOL, such as physical, social, and emotional dimensions. Disease-specific instruments can focus more attention on the special concerns of those affected by particular diseases or conditions of interest. The most widely used instruments assess high-prevalence conditions such as asthma, COPD, and congestive heart failure. More recently, generic instruments have been modified for cystic fibrosis, and there are disease-specific instruments for sleep apnea that have been developed and tested for psychometric standards.

Utility instruments are intended to assess general health using generic measures derived from economic and decision theories. Utilities measure patient preferences for health states and relate them to death (eg, full health = 1, death = 0). Like a generic health index, a utility measure also yields a single numerical estimate of HRQOL that incorporates patient or societal choices for both quality of life and duration of life. The following sections describe the more common HRQOL instruments, providing evidence of their development and use.

**Generic Instruments.** Because of their breadth, generic instruments are well suited to the comparison of HRQOL among different populations or diseases. A particular advantage of generic instruments is that they allow comparison between a particular research or clinical sample and a broader population.[21] In addition, they are more likely to be robust from systematic development and testing in numerous studies.[22] Generic instruments are useful to assess and quantify the effects of comorbidity.[85] A disadvantage of generic instruments is that they often pay little or no attention to specific features of diseases or conditions that can have profound effects on HRQOL. Consequently, generic instruments lack sensitivity and in many cases have limited responsiveness.

The most common generic instruments are the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), the Sickness Impact Profile, the Nottingham Health Profile, and the KINDL for children.

The SF-36 was developed using factor analysis from the much longer batteries of items used in the RAND Corporation's health insurance study experiment.[86,87] The instrument takes less than 10 minutes to complete and can be self-administered. Numerous studies have shown that the SF-36 is psychometrically sound and applicable to a range of settings, which explains why it has virtually become an industry standard in the United States.[43,88–94] The instrument covers 8 domains: physical functioning (8 questions), social functioning (2 questions), role limitations due to physical problems (4 questions) and emotional problems (3 questions), mental health (5 questions), energy and vitality (4 questions), pain (2 questions), and general health perceptions (6 questions). A shorter version, the SF-12, is also available and has potential to capture side-effects and comorbidity and may have wider application in large randomized controlled trials for economic evaluation.[95]

The Sickness Impact Profile includes 12 areas of activity and is sensitive to a wide variety of conditions. It requires about 20–30 minutes to complete the 136 items, providing an overall score and 2 domain scores: physical and psychosocial.[96] The instrument has reported reliability,[97] validity,[23,98–101] and responsiveness,[23,99,101] as well as research use in a clinical trial.[23] It has been compared to clinical indices of asthma and disease-specific quality of life measures, including the AQLQ,[23,98] the St George's Respiratory Questionnaire (SGRQ),[99,102] and the AQLQ-Marks,[100] with established concurrent validity. A recent study found improved HRQOL measured by Sickness Impact Profile, with reduced hyperinflation after lung volume reduction surgery.[103]

The Nottingham Health Profile was developed to evaluate perceived distress across various populations. It is a self-administered instrument and requires 10 minutes to complete the 38 items, covering 6 dimensions: physical mobility (8 items), pain (8 items), social isolation (5 items), emotional reactions (9 items), energy (3 items), and sleep (5 items). Each dimension is based on weights derived from patients and nonpatients (generating scores from 0–100), with the higher score indicating greater health problem. Items were derived from patient interviews and differentiation between illness groups, with reported use in research, including clinical trial.[104] Scores are presented as a profile rather than an overall score.

**Disease-Specific Instruments.** Specific HRQOL measures target certain patient groups (eg, the elderly), diseases (eg, asthma), symptoms (eg, morning headache), or domains (eg, stress). Currently there are numerous disease-specific instruments for a variety of medical conditions, such as chronic lung disease, cancer, arthritis, gastroenterologic disorders, neurologic diseases, heart disease, and a variety of other diseases. A particular advantage of disease-specific HRQOL instruments is the ability to evaluate change in individuals or groups over time. Disease-specific instruments are intended to detect small, meaningful changes in specific patient conditions that generic measures cannot detect because they lack sensitivity. Tables 3 and 4 provide comprehensive lists of the currently available HRQOL instruments for asthma and for chronic respiratory diseases as identified by our search.

When choosing a disease-specific HRQOL instrument for clinical or research use in respiratory therapy, care should be taken to determine that the instrument is valid under the specific circumstances. The following sections provide a brief discussion of disease-specific instruments for asthma, COPD, and sleep-disordered breathing from our review that have sufficient evidence as to the soundness of their psychometric properties.

Table 3. Chronic Respiratory Disease HRQOL Instruments

| | |
|---|---|
| AOMS | Asthma Outcomes Monitoring System |
| AQ 20 | Airways Questionnaire 20 |
| BDI/TDI | Baseline Dyspnea Index/Transition Dyspnea Index |
| CRQ | Chronic Respiratory Questionnaire |
| HOI-Type COPD | Health Outcomes Institute Types Scales-chronic obstructive pulmonary disease |
| MRF 28 | Magueri Foundation Respiratory Failure Questionnaire |
| OSAPOSI | Obstructive Sleep Apnea Patient-Oriented Severity Index |
| PFSDQ | Pulmonary Function Status and Dyspnea Questionnaire |
| PFSS | Pulmonary Function Status Scale |
| RIQLQ | Respiratory Illness Quality of Life Questionnaire |
| SAQLI | Calgary Sleep Apnea Quality of Life Index |
| SGRQ | St George's Respiratory Questionnaire |
| SOLQ | Seattle Obstructive Lung Disease Questionnaire |

HRQOL = health-related quality of life.

**Asthma Quality of Life Questionnaire (Juniper).** The AQLQ uses a 7-point Likert scale to assess HRQOL in asthmatic adults, using 4 domains: symptoms, emotions, exposure to environmental stimuli, and activity limitation.[23,80,98] The AQLQ was originally designed in English (in Canada) as an evaluative instrument to detect small, intra-subject change in HRQOL as an outcome of clinical trials, with demonstrated validity,[80,98,105] reliability,[23,80] and responsiveness.[27,106] However, the AQLQ has been shown to satisfy criteria for a discriminative instrument, capable of detecting change in HRQOL across individuals or groups. Five of the 32 questions are patient-specific. However, the instrument has been modified to a standard version, AQLQ-S, to further facilitate the use of the instrument in large clinical trials and managed care.[107,108] Recently, the AQLQ has been modified further to a short form, the Mini-AQLQ, consisting of only 15 questions and demonstrating satisfactory reliability, responsiveness, cross-sectional validity, and longitudinal validity, although in none of those properties does it perform as well as the original AQLQ.[108,109]

Although HRQOL is strongly influenced by disease severity, demographic and socioeconomic factors may also be important.[110] For example, one study using the SF-36 and AQLQ indicated that socioeconomic status is an additional independent variable influencing HRQOL in asthma, yet it was difficult to separate out the particular effects of race or ethnicity.[110] Another study showed that the AQLQ can be a useful indicator of HRQOL in low-

Table 4 Asthma HRQOL Instruments

| | |
|---|---|
| Adults | |
| AAQ | Attitudes to Asthma Questionnaire |
| ABP | Asthma Bother Profile |
| ACAAI-LQ | American College of Allergy, Asthma, and Immunology-Life Quality |
| AQ20, AQ8 | Airways Questionnaire 20 and Airways Questionnaire 8 |
| AQLQ (Juniper) | Asthma Quality of Life Questionnaire |
| AQLQ-M (Marks) | Asthma Quality of Life Questionnaire |
| ASC | Asthma Symptoms Checklist |
| ASES | Asthma Self-Efficacy Scale |
| ASUI | Asthma Symptom Utility Index |
| HOI-Type Asthma | Health Outcomes Institute Type Scales-Asthma |
| LIFE-A | Life Activities Questionnaire for Adult Asthma |
| LWAQ | Living With Asthma Questionnaire |
| SGRQ | St George's Respiratory Questionnaire |
| Children | |
| AMA | About My Asthma |
| CAQ | Childhood Asthma Questionnaires |
| HAY | How Are You? |
| LIFE-C | Life Activities Questionnaire for Childhood Asthma |
| PAQLQ | Pediatric Asthma Quality of Life Questionnaire |
| Caregivers | |
| PACQLQ | Pediatric Asthma Caregivers Quality of Life Questionnaire |

HRQOL = health-related quality of life

income asthmatics.[111] The AQLQ has been used in a number of research studies, including clinical trials,[112–114] consistently showing validity, reliability, responsiveness, and evaluative and discriminative properties.[102,115–132] One study showed that the AQLQ has similar psychometric properties during hospitalization for acute asthma in adults and subsequently in an outpatient setting.[133] The AQLQ has been translated into a number of languages, including French[120] and Spanish,[134] with translations available from the developers.[80]

**Asthma Quality of Life Questionnaire (Marks).** The AQLQ (Marks) uses a 5-point Likert scale to assess HRQOL of asthmatic adults, using 4 domains: breathlessness and physical restrictions, mood disturbance, social disruption, and concerns for health. It was designed in English (in Australia) as both an evaluative and discriminative instrument to assess HRQOL in asthmatic adults.[100,135,136] Its validity, reliability, and responsiveness have been reported, but an MCID has not been established.[135,136] The modified version of the AQLQ (Marks) has also been reported to be a highly valid measure of asthma-related HRQOL, with good discriminative ability.[137] One study using the AQLQ (Marks) and the SF-36 showed that direct or environmental tobacco exposure prospectively predicted increased health care utilization for asthma and reduced HRQOL in asthma patients.[138] A recent study describes the modification and validation of the Asthma-Specific Quality of Life Questionnaire for Native American Adults, showing its valid use with that population.[139]

**Living With Asthma Questionnaire.** The Living With Asthma Questionnaire (LWAQ) uses a 3-point Likert scale to assess HRQOL in asthmatic adults, using 12 domains: social/leisure, sport, sleep, holidays, work and other activities, colds, mobility, effects on others, medication use, sex, dysphoric states, and attitudes. It was designed in English (in the United Kingdom) as an evaluative and discriminative instrument, and has demonstrated validity,[130,140,141] reliability,[140] and responsiveness.[101,130,142–144] The LWAQ has been used in several research studies,[101,142–144] and a modified, shortened version is available.[145]

**Childhood Asthma Questionnaire.** There are 3 separate pediatric asthma scales grouped under the CAQ.[55,56] The CAQ-A is designed for children age 4–7, the CAQ-B is for children 8–11, and the CAQ-C is for children 12–16. All 3 versions assess quality of life and the level of distress caused by the disease in children. CAQ-A assesses 2 domains: quality of life and distress. CAQ-B assesses 3 domains: active quality of life, passive quality of life, distress and severity. CAQ-C assesses 5 domains: active quality of life, teenage quality of life, distress, severity, and reactivity. Responses are in the form of "smiley" faces for self-report by children or adolescents. However the developers indicate that the questionnaires can be completed with the help of the parent, at least for younger children. The responsiveness and MCID have not been reported, although the original work describes the questionnaire's validity and reliability.[55,56]

**Pediatric Asthma Quality of Life Questionnaire.** The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) is available in both interviewer-administered and self-administered formats, designed in English (in Canada) for asthmatic children age 7–17. The PAQLQ assesses 3 domains: symptoms, activity limitation, and emotional function. The activity domain includes 3 individualized questions in which the patient identifies activities that are limited because of asthma. The instrument has demonstrated reliability, validity, and responsiveness.[49,77] The patient is asked at each subsequent visit how much he or she has been bothered during each of these 3 activities. Showing the patient his or her responses from previous visits has been shown to increase reliability. The PAQLQ has been translated into over 30 languages, including Swedish,[146]

and is available from the developers.[49,77] There is evidence that the PAQLQ is valid and reliable for assessing HRQOL in African-American children, when interviewer-administered.[58] Clinically important improvements in PAQLQ scores have been shown in asthmatic children who participated in a school-based asthma education program.[147]

**St George's Respiratory Questionnaire.** The SGRQ was developed as a disease-specific instrument for use by patients with fixed and reversible airway obstruction to measure overall health, daily life, and perceived well being.[99] The SGRQ was developed in English (in the United Kingdom) and uses 3 sections or domains: Section I (Symptoms) covers symptom severity and frequency; Section II (Activities) covers activities that cause or are limited by breathlessness; and Section III (Impacts) covers social functioning and psychological disturbances resulting from airways disease.[99,102] Sections I and II use a 5-point Likert scale and Section III uses a dichotomous yes/no scale. The instrument has been translated into several languages,[142,148–151] and it compared well to visual analog scales.[152] The SGRQ can be self-administered or interviewer-administered in person or by telephone.[102,143,153] The SGRQ has documented validity,[102] reliability,[99,102] and responsiveness.[99,143] It has been used in several research studies in patients having asthma and/or COPD,[118,122,148,150–155] including clinical trials[143,148] and studies of the elderly.[156] In one study with random allocation of asthma and COPD patients to either a control or intervention group, patient education increased HRQOL measured by the SGRQ among asthmatics but not among COPD patients.[157] A nonrandomized single-cohort study using the SGRQ showed that changes in SGRQ and SF-36 scores correlated and that a modest change in lung function may be associated with clinically important gains in HRQOL.[148] Another study that also used the SGRQ and SF-36 concluded that the HRQOL of COPD patients was more clearly separated by the level of dyspnea than by the American Thoracic Society Disease Staging.[158,159]

**Chronic Respiratory Disease Questionnaire.** The CRQ is an interviewer-administered questionnaire using a 7-item modified Likert scale designed to measure physical and emotional aspects of chronic respiratory disease in 4 domains: dyspnea, fatigue, emotional function, and mastery.[160] The CRQ is a psychometrically-sound HRQOL instrument, having well-documented validity,[160–164] reliability,[160,161,164,165] responsiveness,[26,164–167] an established MCID,[26,166] and good evaluative and discriminative properties.[26,160,163,166] The CRQ was developed in English (in Canada) and has been translated into several languages, including Spanish, French, Italian, and Japanese.[20,22,166,168–172] The instrument and its translations are available from the developers.[160]

The CRQ has been used in several clinical trials showing improvement in HRQOL of COPD patients who received pulmonary rehabilitation,[167,173,174] $\beta$ agonists,[175] prednisolone,[176] or noninvasive positive-pressure ventilation.[177] Additional (though not randomized controlled) studies have used the CRQ and offer evidence on improvements in HRQOL when COPD patients receive pulmonary rehabilitation.[178–181] The CRQ has been used and recently modified for use with cystic fibrosis patients.[182,183]

When used in an outpatient setting, one study indicated that the CRQ performed slightly better than the SGRQ, based on comparative analysis.[184] Factor analysis in another study confirmed the original domain structure of the CRQ, but not the SGRQ.[185] However, the authors concluded that the validity, reliability, and responsiveness did not clearly favor one instrument over the other. Readers should refer to the review by Mahler[186] for additional details about how HRQOL should be measured in COPD patients, using a variety of generic and disease-specific measures.

**Calgary Sleep Apnea Quality of Life Index.** This is a disease-specific, evaluative instrument for patients with sleep apnea to assess aspects of quality of life that can be improved with treatment.[187] Designed in English in Canada, the Calgary Sleep Apnea Quality of Life Index (SAQLI) has 40 questions and assesses 5 domains: role functioning, social interactions, emotional functioning, symptoms, and treatment-related symptoms, using a 7-point Likert scale. It has established validity, reliability, and responsiveness[187] to evaluate the aspects of quality of life affected by sleep apnea and its treatment.[188]

**Functional Outcomes of Sleep Questionnaire.** This is a disease-specific functional status instrument designed to evaluate the impact of disorders of excessive sleepiness on activities of daily living.[189] The instrument was developed in English (in the United States) and uses a 4-point scale (from no difficulty to extreme difficulty) to rate the difficulty of performing an activity. The questionnaire has 35 questions to assess 5 domains: activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome.[186,189] The Functional Outcomes of Sleep Questionnaire discriminates between those seeking medical attention for sleep disorders versus normal subjects and those with obstructive sleep apnea and normal subjects when age- and gender-matched.[189,190] The instrument has reported validity,[189,190] reliability,[189] and responsiveness,[191] demonstrating significant and clinically meaningful effect sizes after treatment.

Table 5 provides further description and information regarding the disease-specific instruments relevant to respiratory care.

Table 5. Supporting Literature for the Disease-Specific HRQOL Instruments

| Disease and Instrument | Literature Reference Number | | | | | |
|---|---|---|---|---|---|---|
| | Validity | Reliability | Responsiveness | Other Properties | Clinical Trials | Other Studies |
| Asthma | | | | | | |
| AQLQ-Juniper | 23, 80, 98, 101, 105, 115–132 | 23, 80 | 27, 106 | 85, 98, 105, 110, 120 | 107, 108, 112, 115 | 110, 111 |
| AQLQ-Standardized | 107 | 107 | 108 | | 107, 108 | — |
| AQLQ-Juniper Mini | 108, 109 | 108, 109 | 108, 109 | — | — | — |
| AQLQ-Marks | 135–137 | 135–137 | 135–137 | 100, 130, 135–137, 139 | — | 138, 139 |
| AQLQ-Marks Mini | 137 | 137 | 137 | — | — | — |
| IWAQ (pediatrics) | 130, 140, 141 | 140 | 101, 130, 142–144 | — | — | 101, 142–145 |
| PAQLQ (pediatrics) | 58, 77, 146 | 58, 77, 146 | — | 58, 77, 146 | 147 | — |
| CAQ (pediatrics) | 55, 56 | 55, 56, 49 | — | 55, 56 | — | — |
| PACQLQ (caregivers) | 49 | — | 49, 77 | | — | 147 |
| COPD | | | | | | |
| CRQ | 160–163 | 160, 161, 164, 165 | 26, 160, 164–167 | 160, 163, 166, 168–172 | 167, 173–177 | 178–184 |
| SGRQ | 99, 102 | 99, 102, 109 | 99, 143 | 99, 102, 142, 143, 148–153, 184–186 | 143 | 118, 122, 148, 150–159 |
| Sleep Disorders | | | | | | |
| SAQLI | 187 | 187 | 187 | 187, 188 | — | — |
| Functional Outcomes of Sleep Questionnaire | 189, 190 | 189 | 191 | 186, 189, 190 | — | — |

COPD = chronic obstructive pulmonary disease
Other terms defined as in Table 4

**Utility Measures.** Utility measures are derived from economic and decision theory to yield a single metric for HRQOL. Utilities are numeric measurements that reflect an individual's beliefs about the desirability of a health condition, the willingness to take risks to gain health, and preferences for time in terms of life expectancy.[192] Utility measures are both discriminative and evaluative. Discriminative utility measures are used to detect differences in HRQOL among groups,whereas evaluative measures assess changes in HRQOL with treatment. One example is the Health Utilities Index, a multi-attribute utility index that yields a single utilities value.[193]

The most common methods for determining health utilities are the standard gamble and the time trade-off. The standard gamble approach asks patients to choose between 2 alternatives: maintaining their current health state or gambling between the potential of full health or death. The probability for full health versus death is varied until the patient is indifferent between the gamble and the chronic health condition. The time trade-off asks the respondent to choose between a longer life expectancy (time) in a lesser health state or shorter life expectancy in a perfect or excellent state of health. Preference values are determined implicitly, based on individual responses to decision situations. For example, "Would you rather live 10 years with a tracheotomy or 5 years in perfect health?" or "For how many years of perfect health would you trade 10 years of living with your disease as you currently feel?" The time in the state of perfect health is varied until the respondent is indifferent between the choices. A score of zero is equivalent to being dead; a score of 1 is equivalent to perfect health. The measured values for time trade-off are reliable and stable; however, this overall measure of HRQOL does not permit determination of which aspects of health (emotional, social, or physical) are most important to the individual.

Utilities are increasingly used to make cost comparisons and to evaluate the cost-effectiveness of health care.[194,195] The most common assessments include cost-utility analysis and cost-value analysis. Cost utilities analysis incorporates utilities with quality-adjusted life years (QALYs). QALYs combine utility, gains in quality of life, and life years in a single metric. Such an analysis of health makes assumptions that younger lives are more valuable than older lives, since geriatric patients will achieve a lower QALY because of fewer remaining life years. There is also the assumption that quality of life is lower whenever there is disability, based on how the calculations are made. However, there is a subjective component to quality of life that the QALY metric cannot capture. Consequently, there have been developments in using cost-value analysis, which assesses cost-benefit, cost-effectiveness, and disability-adjusted life years rather than QALYs.[42,43]

## Summary

Assessment of HRQOL is changing the medical paradigm from a disease-centered approach to a patient-cen-

tered approach. Increasingly, HRQOL assessment has become the tool to increase patient involvement in medical care and decision-making. For example, HRQOL assessment can be used to improve detection of physical and psychosocial impairments in persons with acute or chronic respiratory conditions. In addition, HRQOL assessment may identify patient needs and areas of understanding to tailor care for individual patients and improve adherence.

Assessment of HRQOL has also proven to be a useful tool to clinicians to inform medical decision-making:

1. When there is a choice among multiple clinically-effective strategies

2. When there are trade-offs between risk, benefit, survival, and cost of a therapy

3. When choosing between therapies for which there is only a small difference in survival between the therapies, or

4. When considering treating patients with a symptomatic or mildly symptomatic disease

Assessment of HRQOL is also valuable to health care policy makers and epidemiologists when making decisions regarding strategic planning and initiatives to improve the costs, outcomes, and accessibility to health care delivery systems. Increasingly, HRQOL assessment is an important component of comprehensive health care delivery, affecting how effectiveness is evaluated from societal, epidemiological, economic, provider, and patient points of view. Consequently, RTs should become familiar with the most common HRQOL measures and seek to incorporate them into their clinical research and practice, using sound methods for selection, use, and interpretation of those outcomes.

### ACKNOWLEDGMENTS

We thank Patricia McShane for her valuable assistance with the literature searches and preparation of tables.

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### Discussion

**Rowe:** When you talked about the minimally clinical important difference (MCID), you stated that you were looking for, or that one of the requirements was, a consensus among most clinicians. We generally don't use consensus among clinicians. We use the information from patients; we ask them whether they felt they were better and then we determine the minimally clinical important difference (MCID) from that. That's from the patient's perspective. I wonder if you could comment on that issue.

**Mishoe:** The patient perspective is important. What I mean by consensus is the HRQOL data linked back to clinical variables such as improvement in $FEV_1$ or peak flow—how much change, then, is really important? The patient perspective is important, but in looking then from the statistical data, there needs to be some agreement as to how much change. So maybe you could elaborate on how you're doing this and reporting it in your work.

**Rowe:** If we were to use change in pulmonary function, nothing would be important, because these patients' pulmonary function doesn't seem to change. But they report a marked difference in their quality of life—how they are able to interact with the environment, their symptoms, their emotional domain—they clearly have differences in quality of life. They can detect that, so then we can look at it. Basically, what we do is report the quality of life or collect the quality of life information and then ask them, "Compared to the last time we asked, are you better, the same, or worse?" Then you examine ranges of improvement and decide what is the MCID for the patient. So if the scores don't change—no difference between the 2 time periods—that wouldn't be important to the patient. I couldn't tell you that as a clinician because I don't have asthma. You could go around a table of researchers and ask them for their consensus on that change. They couldn't tell you. It would be a guess. Whereas patients can tell you very clearly that they felt better or worse, and over that period of time you can determine what the MCID is. I think the problem with something like the standard error of the mean is that it is completely dependent on sample size. If you have a huge sample size such that the report suggests one standard error of the mean difference is minimally clinically important, that would not make much sense to the patient.

**Mishoe:** I think because you're using a very responsive, sensitive instrument, you're able to do that. When you get into the generic measures, I think there is some application of what's a clinically important difference by using the standard error of the mean. Any other reactions or comments regarding that point?

**Guyatt:** Careful! I don't think you actually mean the standard error of the mean, which, as Brian [Rowe] has pointed out, is dependent on sample size. What Wyrwich and her colleagues are talking about is the standard error of *measurement*, which is something different and is not dependent on sample size.[1,2]

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**Mishoe:** You're right; I mean the standard error of measurement, which is the standard deviation times the square root of one minus the reliability coefficient. Thank you. Big difference!

**Flemons:** About the MCID, I don't believe that it has ever been evaluated for a generic instrument, and I'm not sure that a generic instrument has ever been developed to measure change over time. That, perhaps, is the most frustrating thing, because everybody loves the SF-36; they love to quote changes in the SF-36. But I've never found anybody who can interpret what those changes mean. And yet they're quoted over and over again because it's an off-the-shelf instrument. You don't even need to understand what quality of life is to use it. Disease-specific quality of life instruments, such as the ones Gordon [Guyatt] and his colleagues have developed, offer interpretability. I don't know that there's a real role for interpreting changes with therapy for a generic quality of life index.

**Mishoe:** The generic measures are useful in looking at co-morbidity and differences between groups, but not necessarily good for intra-individual change. There's still usefulness for tools such as the SF-36, but in terms of evaluating a treatment and evaluating it in a patient group, then a disease-specific instrument needs to be included.

**Flemons:** With respect to the SF-36, if on average patients improve 20 points in 3 out of 8 domains, since each of the domains is scored differently, I have absolutely no idea whether, overall, patients are feeling better or not. Unless we can boil it down more specifically I don't think we're ever going to really utilize those data. I would guess that 95% of the data published right now is on those kinds of measures that, for my money, are uninterpretable.

**Mishoe:** I would agree with that, and maybe we've spent way too much time and effort on development and use of generic measures, and not enough time and attention on disease-specific measures that can really capture what we're interested in from an evidence-based perspective, research perspective, and more importantly a clinical perspective.

**Flemons:** I'd like to make one other point, which is that what most people would like to know is, in their experience, what percentage of patients they treat are actually going to experience a benefit from a particular treatment? Using an MCID, you can actually get at that percentage, but it's rarely reported. We continue to report mean improvements with this measurement and that measurement, but that doesn't really help the everyday practitioners to know how many patients will actually benefit from it. That would be the other thing I would encourage for the outcome movement—to report results in that respect so they're more user-friendly for the people who use the information to guide clinical decisions.

**Ellrodt:** How long do these questionnaires tend to be? Are they useful in clinical care or are they useful only as part of trials? By clinical care, I mean in a doctor's office. If you have a large asthma population, could you imagine using even some of these disease-specific questionnaires to help guide your management in that population or in a disease management program?

**Mishoe:** I do think the really long instruments are more reliable, but the burden is too big from the respondent's perspective, as well as administrative. One of the ways to have a shorter instrument that is still reliable and responsive is to have more choices for each particular question by using a VAS [visual analog scale] or 7-point scale. That is one strategy that has a lot of promise. The first time I ever used the Pediatric Asthma Quality of Life Questionnaire, and there were 7 different responses, I thought "A person can't discriminate across these seven, especially a child." I had my doubts, but once you've used instruments like that you really can appreciate them. Even the SF-36 is now available in a shorter form, the SF-12, and probably the SF-3 next. Who knows? There have been attempts to make the instruments shorter and still meet the needs of psychometrics as well as the clinical applications.

**Guyatt:** Given the time most patients spend in the doctor's waiting room, I don't think the length of the instrument is the crucial issue. You can have people fill it out while sitting there, and it gives them something to do. The question of whether that adds anything to the clinical assessment is one that has not been thoroughly studied, and I think the issue—I start to wonder whether this is supposed to be a substitute for talking to your patient. To what extent can clinicians gain the same information during their conversations with their patients? Where it might have potential is with children. What extent does the pediatrician get independent information from the parent and child? Because our data with these questionnaires is that one can get independent information from these questionnaires that sometimes differ between the parent and the child. The issue that re-

mains open is how much do you actually gain by their administration and interpretation in addition to the usual interaction between patients and clinicians?

**Mishoe:** During the wait time the patient could complete the instrument and then the provider could review it as a point of discussion, since the time for patient interaction is so limited. I think that's an excellent clinical applicability of HRQOL measures.

**Guyatt:** It may be. I would still like to see evidence that it improves things, rather than the intuitive equivalent of physiologic rationale that you've offered.

**Mishoe:** In response to Gordon Guyatt that we do need the evidence and we should pursue that evidence; intuitively it makes sense. When you talk about HRQOL, there is a tremendous clinical applicability issue beyond the HRQOL research issues for use of the information. That would be a point for future research, because the evidence is currently lacking.

# Translating Evidence into Practice: Pursuing Perfection in Pneumococcal Vaccination in a Rural Community

Daniel M Doyle MD, Robin Dauterive MD, Kenneth H Chuang MD, and A Gray Ellrodt MD

Introduction
Challenges to Translating Evidence into Practice
Considerations in Developing a Behavior-Oriented Program to Translate Evidence Into Practice
  General Issues
  Frame the Program: "Pursuing Perfection" Rather Than Just Improving Performance
  Assess Opportunity to Improve Health Care and Present in Real-World Clinical Terms
  Diagnose Specific Behavioral Barriers to Success
  Knowledge
  Attitudes
  Behavior
Stategies (Treatment Options) to Overcome Barriers to Successful Clinical Guideline Implementation
  Development of Clear, Actionable Guidelines
  Dissemination and Implementation Strategies
Development and Implementation of a Hospital-Based Program to Improve Pneumococcal Vaccination Rates
  Selection of Program
  Setting Goals
  Assessment of Barriers to Adherence for the Hospital Phase
  Knowledge
  Attitudes
  Behavior
  Multidisciplinary Rounds
  Interim Results
  Next Steps for a Community-Based Program
Summary

There are many challenges to effectively and efficiently translating evidence into practice. Potential strategies include (1) training more evidence-based practitioners in the art and science of evidence-based medicine, (2) enhancing the quality and availability of systematic reviews, and (3) more effectively linking evidence-based practitioners and evidence users through comprehensive behavioral change initiatives. Herein we explore the third strategy and highlight the key elements of success for a program using behavioral change strategies. We present a clinical model based on clear understanding of the "problem," a systematic approach to diagnosis, selection of scientifically sound treatment options, and effective evaluation with appropriate modification of the treatment plan. A successful program begins with effective team leadership, the expression of a clinically compelling case for change, and commitment to the pursuit of perfection in the delivery of key evidence-based interventions. The team must then diagnose behavioral barriers to change, using a systematic approach based on a published rigorous differential diagnosis framework. This diag-

**nostic step provides the foundation for selection of effective dissemination and implementation strategies (treatments) proven to improve processes of care and clinical outcomes. Finally the team must evaluate progress toward perfection, reviewing interim data and adjusting the treatment regimen to newly diagnosed barriers. We then present a specific project (improving pneumococcal immunization rates in our rural community) and interim results to demonstrate the use of the framework in the real world.** *Key words: pneumococcal immunization, evidence-based medicine.* [Respir Care 2001;46(11):12581258–1272]

## Introduction

Physicians and other health care practitioners face multiple challenges in providing state-of-the art care for their patients. One of the most daunting ongoing challenges is the translation of best evidence from the medical literature into the day-to-day practice of busy clinicians. This challenge is particularly important in the complex and rapidly changing worlds of internal medicine and pulmonary medicine.

The gap between evidence and practice has recently been called a chasm.[1] The realistic potential solutions to bridging this divide (Fig. 1) include:

1. Training more practitioners in the art and science of critical appraisal. Unfortunately this will be challenging, with the observation that 95% of practitioners are not enthusiastic about this approach.[2]

2. Improving the quality and accessibility of evidence-based summaries.[3]

3. Training selected physicians in the skills of evidence-based medicine (EBM), including searching, critical appraisal, enhancing the breadth and depth of current evidence summaries, and effectively utilizing behavior change strategies.[1,3]

Herein we focus on the behavior change strategies of this complex challenge. We will explore the barriers to changing practitioner behavior and approaches to overcoming those barriers. As an example we will use our preliminary experiences in developing a health-system-wide program to improve pneumococcal vaccination rates in our rural community. Specifically, we will:

1. Discuss the general challenges to changing practitioner behavior.

2. Focus on physician-identified barriers to implementing guidelines, using the systematic approach described by Cabana et al.[4] This section thus presents an approach to differential diagnosis of barriers to adherence.

3. Present the potential treatment strategies to overcome the barriers. We will begin with a general overview of dissemination and implementation strategies and tactics for which there is compelling evidence from randomized controlled trials and multiple meta-analyses. We will then link specific guideline development, dissemination, and implementation strategies to overcome the barriers to change.

4. Present specific strategies for improving pneumococcal vaccination rates in various settings, including ambulatory, emergency room, and hospital. We will use our own health system and observations from our initial hospital-based efforts to elucidate an evidence-based approach to practice change.

Herein the term "guideline" means the expression of recommendations for interventions. Readers should understand that the terms "guideline" and "recommendation" include practice parameters, algorithms, and even consensus statements. The more rigorous definition of "guidelines" and the operational definition for this paper is: "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[5] These guidelines, recommendations, and practice parameters are but an important first step in a comprehensive approach (program) to improve clinical management and health outcomes. Herein we assume that a multidisciplinary team has been assembled and will guide the effort. In addition we are assuming the presence of credible leadership for the effort. These are important assumptions!

## Challenges to Translating Evidence into Practice

In this section we explore the nature of barriers to evidence-based care, setting the stage for a discussion of behavioral strategies to overcome those barriers. A survey was performed of British general practitioners' perceptions "of the route to evidence-based medicine."[2] This article summarizes the results of a questionnaire distributed in 1997 to 25% of all general practitioners in the

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A version of this paper was presented by Dr Ellrodt during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20-22, 2001, Banff, Alberta, Canada.

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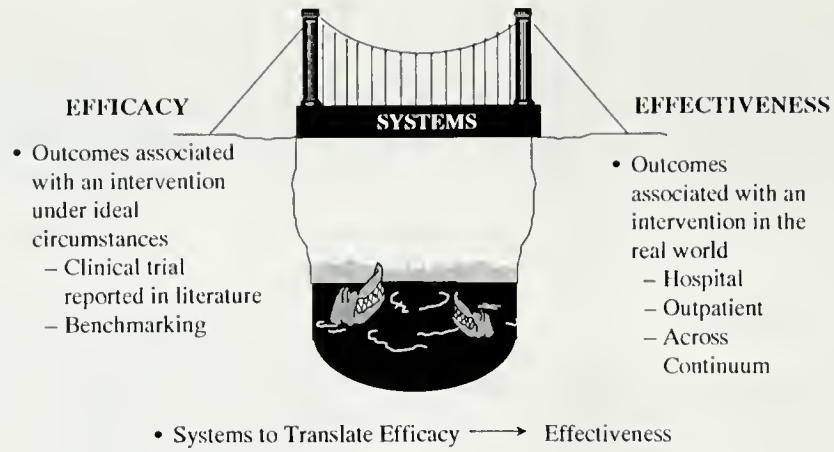
EFFICACY
SYSTEMS
EFFECTIVENESS
• Outcomes associated with an intervention under ideal circumstances
– Clinical trial reported in literature
– Benchmarking
• Outcomes associated with an intervention in the real world
– Hospital
– Outpatient
– Across Continuum
• Systems to Translate Efficacy ⟶ Effectiveness

Fig. 1. Bridging the gap between efficacy and effectiveness.

former Wessex region in south England. The authors concluded that:

- Most practitioners welcomed EBM and agreed that it would improve care.
- There was a low level of awareness of extracting journals and other resources summarizing the evidence on a particular topic.
- The major perceived barrier to evidence-based practice was lack of time.
- At the time of the survey few practitioners (17%) had access to MEDLINE or the World Wide Web.
- Although most had some understanding of EBM terminology, few felt comfortable attempting to explain terms and concepts to others.
- Only about 5% of respondents felt that learning the basic skills of EBM, including "... identifying and appraising the primary literature or systematic reviews," was the most appropriate method for advancing from opinion-based medicine to EBM.
- A majority (57%) thought that the most appropriate way to move from opinion-based medicine to EBM was "using evidence-based guidelines or protocols developed by colleagues for use by others."[2]

Although one could question the generalizability of those observations to American primary care physicians and pulmonologists, it is unlikely that United States or Canadian practitioners have any more time or enthusiasm for learning the basic skills of EBM. Indeed, these observations rang true to some of the innovators and leaders in EBM at McMaster University when reflecting on their own experiences with trainees.[3]

Therefore we will focus our review on the barriers to implementing clinical practice guidelines and the potential behavioral methods for overcoming these real or perceived barriers. We will move from a general review of barriers and strategies to overcome them to a specific discussion of improving rates of pneumococcal vaccination.

## Considerations in Developing a Behavior-Oriented Program to Translate Evidence into Practice

### General Issues

In any health care organization, numerous opportunities exist for program development. When a new program is brought forward, it is reasonable to assess the general issues summarized in Table 1. These issues should be addressed early rather than after the program has been developed, to be sure insurmountable barriers are not encountered far into a project. Issues such as the existence of a real opportunity to improve care and the settings in which the program will be implemented must be assessed early. In addition, the goals must be assessed, effective leadership is essential, and institutional culture must be reviewed. These are some of the most important challenges for any project. Again, we will assume that a multidisciplinary team is in place with effective leadership and that this group will handle many of the decisions and approaches. In general we recommend that the complete team not be formed until an assessment of opportunity has been refined.

### Frame the Program: "Pursuing Perfection" Rather Than Just Improving Performance

The framing of goals in a specific project or in all institutional projects is of utmost importance. In our experience, many performance improvement projects, even those based on strong evidence from the literature, are targeted at improving performance from a baseline level to

Table 1. General Issues in Developing a Program to Translate Evidence into Practice

| Issue | Comment |
|---|---|
| 1. Is there a substantial opportunity to improve care? | If no real opportunity exists, move on to next project. |
| a. What is baseline performance? | If performance is already excellent, opportunity may be small. |
| b. What does evidence state opportunity would be? | Derive from number needed to treat, absolute risk reduction, current performance compared to perfection. |
| 2. What should goal be? | Perfect performance |
| | 100% adherence with evidence-based recommendations in eligible patients |
| 3. Are there personnel and evidence-based leaders for the project? | Beware lack of leadership. |
| 4. What are the settings (eg, hospital, clinics, private practices)? | Different settings may require different strategies. |
| 5. Who needs to be involved to make project successful? | Consider physicians, other practitioners, pharmacy, administration, and house staff. |
| 6. What are the practitioner specific barriers to translating evidence into practice? | Use Cabana et al[4] framework. |

a benchmark or goal well below 100%. For many evidence-based guidelines, a goal of less than 100% adherence for eligible patients makes very little sense. For example, the evidence supporting acetylsalicylic acid, $\beta$ blockers, and angiotensin-converting enzyme inhibitors acutely and at discharge for eligible patients admitted with acute myocardial infarction is compelling. To aim for 90% adherence in those patients from a baseline of 70–80% is difficult to support. We now frame such guidelines as medical errors. In such cases we consider failure of prescription of these essential interventions errors of omission and therefore "pursue perfection" (this term was used in a grant from the Robert Wood Johnson Foundation) rather than just improvement.

This approach requires broad institutional buy-in and framing of such projects as nonpunitive and as issues of systems failure, not individual failure.[6] Addressing goals up front will be particularly important in overcoming several of the specific barriers addressed below.

## Assess Opportunity to Improve Health Care and Present in Real-World Clinical Terms

Before pursuing a project, an attempt should be made to quantify the opportunity in terms that are meaningful to members of the organization. In general, for clinicians this means improvements in clinical outcomes, and for the finance/operational departments it means real "bottom line" savings that can be captured in budgets.

For clinicians we have found that expressions in terms of relative risk, relative risk reduction, and even absolute risk reduction and number needed to treat are too abstract for evidence users. Therefore, based on anecdotal experience,[7] we express opportunities in terms such as mortality prevented or morbidity avoided. We frame these calculations based on current performance compared to perfect performance. For example, when we were developing our stroke unit at Berkshire Medical Center, we projected clinical impact based on current number of stroke patients treated and a meta-analysis of the impact of stroke units and teams. We did not have a stroke unit or team at the beginning of the project. We concluded that the absolute risk reduction for death with a stroke unit compared to our usual care was 4.5% and for dependence or death 6.4%. This meant that, given 225 admissions per year with stroke, we could prevent 10 deaths in our community and prevent about 5 dependencies.[8]

## Diagnose Specific Behavioral Barriers to Success

As the multidisciplinary team begins program design it should perform an inventory of specific practitioner barriers to guidelines. Many but not all of these will center on physicians. The recent systematic review by Cabana et al may be helpful as a checklist to assess potential barriers and guide program design. A barrier was defined as ". . . any factor that limits or restricts complete physician adherence to a guideline."[4] The article focuses on physician adherence to "guidelines." The term "guideline" was broadly defined in that article and included clinical practice guidelines, practice parameters, clinical policies, or national consensus statements.[4] The authors developed a helpful framework through a systematic literature review. The general framework is summarized below and presented in Table 2 as a checklist.

The team must remember that the framework for barrier assessment was developed using many studies of out-patient and nonacute care interventions. The framework is based on a sequence of behavior change from knowledge, through attitudes, to behavior. This framework is consistent with literature describing successive "voltage drops" from knowledge to attitudes to behavior. In one study examining change in performance in cesarean section prac-

Table 2. Framework for Assessing (Diagnosing) Physician Barriers

| Barrier | Description | Present/Absent |
|---|---|---|
| Knowledge | | |
| 1. Awareness | Unaware recommendations exist | |
| 2. Familiarity | Unaware of details of recommendations | |
| Attitudes | | |
| 1. Agreement with potential specific recommendations (guidelines) | Evidence interpretation<br>Patient applicability<br>Confidence in developer | |
| 2. Agreement with guidelines in general | For example: too cookbook, rigid, biased, impractical | |
| 3. Outcome expectancy | Performance of recommendations will not lead to desired outcome | |
| 4. Self efficacy | Physician cannot perform recommendations | |
| 5. Motivation | Habit/routines | |
| Behavior | | |
| 1. Patient factors | Patient preference vs recommendations | |
| 2. Guideline factors | Characteristics (eg, complexity), contradictory guidelines | |
| 3. Environmental Factors | Lack of time<br>Resources<br>Organizational constraints<br>Financial disincentives<br>Malpractice risk | |

(Adapted from Reference 4)

tice based on a Canadian Consensus Statement, investigators found:[9]

*Knowledge.* About 90% of study physicians were aware of the recommendations, but when tested on detailed knowledge (familiarity), only 3% were able to answer all 8 questions correctly.

*Attitudes.* About 90% agreed with the recommendations.

*Behavior.* Thirty-four percent of study physicians reported changes in practice consistent with guideline recommendations.

*Outcomes.* On chart review, almost no change in practice was detected.

Further validation of the Cabana framework and real world utility will be required. Nevertheless, as the team develops recommendations and designs strategies, referral back to the framework may be helpful to assure that the team has addressed most or all issues. It is very likely that multiple barriers will be identified as the team moves through the sequence. It is also highly likely that the behavior change strategy will need to be modified in real time. Specifically, as the team moves from overcoming knowledge barriers to attitude and behavior barriers, different and potentially more intensive interventions may be required and adjustments in strategy will be needed. Finally, as the team examines interim data, it will need to refine its strategies as new barriers are identified. A more specific description of barriers derived from the Cabana article[4] follows:

### Knowledge

*Lack of awareness* indicates that the physician does not know a guideline exists. This is understandable given the multiple recommendations and sources confronting the busy practitioner.

*Lack of familiarity* suggests that although physicians may be aware of a guideline they do not have sufficient knowledge of the details to act on the recommendation.

### Attitudes

*Lack of agreement with a specific guideline* includes multiple subcategories such as interpretation of the evidence supporting the guideline, belief that the benefits would not outweigh the risks or costs, applicability to a patient population, oversimplification, or lack of author credibility.

*Lack of agreement with guidelines in general* includes general views about guidelines, such as that they represent "cookbook" medicine, reduce autonomy, are not practical, are biased, or lack credible authors.

*Lack of self-efficacy* refers to the belief that the practitioner cannot effectively perform the intervention because of lack of preparation or self-confidence. This may be particularly important in preventive health counseling and education.

*Lack of outcome expectancy* refers to the belief that a specific intervention will not lead to a particular conse-

quence. Thus, although a physician may be confident that she can perform the intervention (self-efficacy), she is not convinced it will help the patient. Balancing the individual patient and the population impact may be an important consideration.

*Lack of motivation or inertia of previous practice* addresses the issue of readiness to change. The model has been well described and includes a continuum of steps including pre-contemplation, contemplation, preparation, action, and maintenance. Many physicians are in the pre-contemplation phase and thus are not motivated to change.

### Behavior

Behavior includes 3 general areas:

*Guideline factors* include convenience and ease of use. This may be related to clarity of presentation or availability at the time of use. In addition, the availability of conflicting guidelines may be a substantial barrier to adherence.

*Patient-related barriers* derive from patient preferences and values. As such, they may or may not be modifiable. This issue gets at a fundamental principle of EBM: the need to clearly identify and frame a health care decision, address the benefits and risks of an intervention, educate the patient and family, and then integrate information with patient values to drive informed adherence.

*Environment-related barriers* are often issues out of the physician's direct or even indirect control. As such, changes in systems of care may be required. These include financial disincentives, insufficient time, lack of reminder systems or counseling resources, or even perceived increases in malpractice liability.

## Stategies (Treatment Options) to Overcome Barriers to Successful Clinical Guideline Implementation

Before proceeding to selection of the multiple treatment options it is reasonable to again ask:

Do we have the necessary leadership for this program (preferably an evidence-based opinion leader)? Do we have agreement that the pursuit of perfection is the goal of this program? Do we have a compelling case to engage the practitioner community, expressed in real terms such as potential lives saved?

If the answer is yes to all those questions, the team can proceed. There is a substantial body of literature about interventions that can be used to improve adherence to guidelines, which includes multiple rigorous randomized controlled trials and meta-analyses. They can be divided into 3 general areas:[10,11]

1. Effective guideline development addresses issues of evidence synthesis, expression, and local input.

2. Effective guideline dissemination includes the communication of information to improve knowledge or skills.

3. Effective guideline implementation refers to more active dissemination and includes strategies to overcome behavioral and attitudinal barriers.[4]

### Development of Clear, Actionable Guidelines

The process by which the team determines which recommendations it will make, the rigor of the development process, and the strength of evidence may well determine acceptability by clinicians. Several studies have addressed the issue of guideline content and development process, and have concluded that:

1. Guidelines are more likely to be followed if they are evidence-based.[12]

2. Guidelines are less likely to be followed if they are controversial, incompatible with current values, or vague and nonspecific.[12]

3. Guidelines are less likely to be followed if they demand extra resources, require new knowledge or skills, or provoke negative patient reactions.[12]

4. Guidelines developed internally have a higher probability of being effective than external local or national guidelines.[11,13]

Thus there is support from both observational studies[12] and systematic reviews[11,13] that the *process* of guideline development is important. The development team should keep in mind that local development does not mean ignoring national recommendations from credible organizations using rigorous development methods. It does imply, however, that national recommendations require local review and endorsement before they will be broadly accepted. The guideline development process is one of the key areas in which real expertise in identification of evidence-based resources, searching, and critical appraisal is required. Ideally the person leading the local guideline development process is an evidence-based practitioner, not just an evidence user.[3]

### Dissemination and Implementation Strategies

The development team has multiple options for disseminating and implementing its recommendations (guidelines). The simple reminder that "guidelines do not implement themselves"[5] should serve as a warning that the hard work of making guidelines work has now begun. Several approaches to categorizing interventions have been developed. Grimshaw and Russell[11] have separated dissemination and implementation strategies. In its approach, dissemination includes communication to front-line practitioners in a manner that sets the stage to change attitudes and behavior. Implementation can be considered more reinforcing and active in the overcoming of barriers.[4]

In reality, potential interventions are probably along a spectrum and are often used in combination. There is extensive, rigorous literature addressing dissemination and implementation. The focus has been on changing practitioner behavior (not just physicians). There are multiple dissemination and implementation strategies from which to choose. These can be considered treatment options for the barriers diagnosed through the Cabana framework described above. Since the team knows which critical interventions will be implemented, it can custom tailor its dissemination and implementation strategies for the practitioners and systems within its organization. Table 3 presents an overview of barriers to successful implementation and potential strategies to overcome them. Figure 2 summarizes the elements of a successful behavioral change program.

An important first step in any project is identification and development of credible leadership. Local opinion leaders are essential to success at many phases of the program. Although the literature has emphasized their role in dissemination, they can address and solve multiple dissemination and implementation issues. (Adapted from Reference 4.)

*Local Opinion Leaders.* These individuals are influential and well respected providers who support the program and encourage their colleagues to participate. Although in the literature their impact has not been consistent, they may improve adherence to process of care measures. Their impact on outcomes is less clear.[13–16] In one randomized controlled trial of opinion leaders in 37 Minnesota hospitals, individuals were selected using a validated tool. They focused on barriers to change and comparative performance of aspirin, $\beta$ blockers, lidocaine, and thrombolytic use in acute myocardial infarction. In the opinion leader group a statistically significant improvement was noted in

Table 3. Framework for Overcoming (Treating) Specific Barriers to Change

| Challenge/Barrier/Diagnosis | Strategy/Treatment Option | Reference |
|---|---|---|
| General | | |
| 1. Leadership (evidence-based practitioner) | Opinion leaders | 13–15, 16, 17 |
| 2. Case for change | Express in real-world terms, knowledge baseline information | 7<br>1 |
| | Pursue perfection | |
| Knowledge | | |
| 1. Awareness | Traditional CME | 11, 13–15, 18–21 |
| 2. Familiarity | Interactive meetings | 11, 13, 14, 22, 23 |
| | Case-based CME | 24, 25 |
| | Academic detailing | 13–15, 25 |
| Attitudes | | |
| 1. Agreement with potential specific recommendations (guidelines) | Academic detailing | 13–15, 25 |
| | Case-based CME | 24, 25 |
| | Interactive sessions | 11, 13, 14, 22, 23 |
| 2. Agreement with guidelines in general | Multifaceted interventions | 13–15, 18, 26 |
| | Academic detailing | 13–15, 25 |
| 3. Outcome expectancy | Case for change | 7 |
| 4. Self efficacy | Small case-based | 13–15, 25 |
| | Academic detailing | 27–29 |
| | Complementary providers | |
| 5. Motivation | Multifaceted interventions | 13–15, 18, 26 |
| | Complementary providers | 27–29 |
| | Case for change | |
| | Operational incentives | 30–33 |
| Behavior | | |
| 1. Patient factors | Patient-targeted interventions | 13–15 |
| 2. Guideline factors | Academic detailing | 13–15, 25 |
| | Operational incentives | 30–33 |
| | Interactive meetings | 11, 13, 14, 22, 23 |
| 3. Environmental factors | Multifaceted interventions | 13–15, 18, 26 |
| | Operational incentives | 30–33 |
| | Complementary providers | 27–29 |
| | Concurrent reminders | 11, 14, 15, 25, 34, 35 |

CME = continuing medical education.

# PURSUING PERFECTION: BEHAVIORAL FRAMEWORK

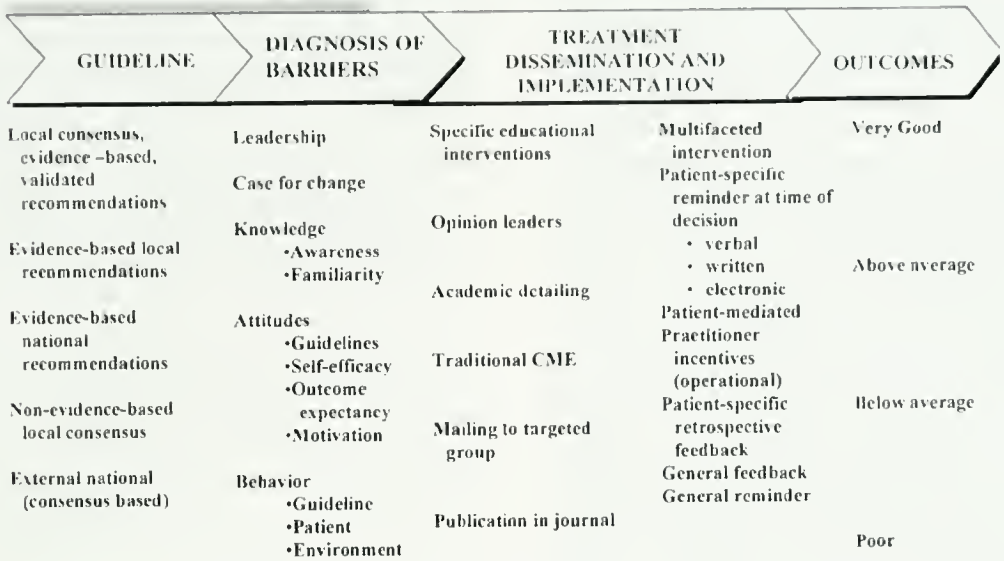


Fig. 2. Behavioral framework for pursuing perfection. This framework assumes effective leadership (preferably an evidence-based practitioner). It then serves as a guide for a multidisciplinary team to: (1) Identify rigorous guidelines and develop local consensus around them; (2) Proactively diagnose behavioral barriers through review of column 2. (3) Select dissemination and implementation strategies proven to be effective. Effective strategies are at the top of the dissemination and implementation columns. By developing acceptable, evidence-based guidelines, diagnosing behavioral barriers, and "treating" them with effective dissemination and implementation strategies, outcomes are very likely to improve for patients. CME = continuing medical education. (Adapted from Reference 4.)

appropriate use of $\beta$ blockers and aspirin, but no change was observed in the use of thrombolytics or lidocaine.[17] The importance of leadership in these programs linked to improved implementation systems is paramount. Although not clearly stated in the literature, a refinement of opinion leader qualifications to include being evidence-based practitioners, not just evidence users, may be important and worthy of study.

The team can choose from the following interventions (treatment options) for dissemination:

*Interactive educational meetings* include active discussion, role-playing, and training exercises in a conference setting. Such meetings have consistently demonstrated effectiveness in promoting behavior change.[11,13,14,22,23]

*Case-based continuing medical education.* Information is provided to health care practitioners as clinical case scenarios with active discussion. This approach is consistently effective.[24,25]

*Academic detailing.* This adaptation of pharmaceutical industry detailing uses trained persons who meet with providers in their own practice environment to provide information and promote discussion. This approach has been effective in changing prescribing habits in the pharmaceutical industry. The identification and targeting of barriers to change may be useful.[13–15,25]

*Printed educational materials* include recommendations or guidelines that are mailed, hand-delivered, or electronically or audio-visually presented to providers. Alone, these materials have not been shown to change practice, but when used as one component of a multifaceted intervention, they have been successful.[11,14,15,36]

*Traditional continuing medical education* that uses didactic lectures to convey information to health care providers has not been shown to improve clinical outcomes. This does not mean that a team should not consider this approach as part of a more comprehensive strategy, but traditional continuing medical education alone will not result in improved performance.[11,13–15,18–21]

In addition the team should consider the following implementation strategies. If the team foresees multiple substantial barriers to successful implementation, a multifaceted approach should be considered. If the team diagnoses a few specific barriers, a more "surgical" approach, using a single implementation strategy, may be appropriate. Possible implementation strategies include:

*Multifaceted approaches* employ a combination of dissemination and implementation approaches to influence provider behavior. These may include dissemination strategies linked to implementation strategies. For example, an opinion leader could provide concurrent feedback during rounds. A multifaceted approach has consistently demonstrated effectiveness. It is unclear, however, which combination of strategies is most effective.[13–15,18,26]

*Concurrent reminders* are messages to practitioners to perform a given intervention. They can be delivered in writing, verbally, or through a computerized interaction. Guidelines using patient-specific reminders at the time of consultation are likely to be effective. Written and electronic reminders appear to be equally effective. Verbal reminders have not been as well studied.[11,14,15,25,34,35]

*Computerized tools* involve feedback, provision of guidelines or algorithms, and computer-assisted diagnosis and medical record keeping. Computerized reminders have been most completely studied in the out-patient setting and have been shown to be effective. Computerized drug algorithms are effective in improving physician prescribing. Computer-based clinical decision support systems for diagnosis have not been effective.[34,37–40] A computer-assisted management program for antimicrobials improved clinical and financial outcomes in the intensive care unit.[41]

*Patient-targeted interventions* have also been referred to as patient-mediated interventions. Specific information is sought from or given to patients, who then stimulate change in their providers. This approach has been used by the pharmaceutical industry in their direct-to-consumer marketing. Although some variability in effectiveness has been seen in trials and systematic reviews, this is in general an effective approach.[13–15] This approach might be considered in improving follow-up care in areas such as adherence to medication regimens at home or enhancing adherence to immunization recommendations.

*Nonfinancial operational incentives* include changes in the patient care system that enable the provider to improve patient care. Such approaches can include "total quality management/continuous quality improvement" programs involving multidisciplinary teams using systematic approaches. They may implement system, policy, or procedure changes in care. Changes that include standing orders have been effective, but other interventions surrounding the standing orders were included in the trials.[30–33]

*Complementary practitioners* are nonphysicians who take a major role in patient management. A limited number of studies support the expanded role of pharmacists in patient counseling and physician education.[27] Kollef et al compared protocol-directed ventilator weaning (conducted by nurses and respiratory therapists) to physician-directed weaning, and found that protocol-directed weaning gave better outcomes.[28] In a study by Ely et al, a multidisciplinary team including physicians, nurses, and respiratory therapists screened potentially eligible patients for weaning suitability and found better outcomes.[29]

*Case management* is the coordination, facilitation, and management of care delivery across the health care continuum. Studies of case management have reported variable effectiveness in improving patient outcomes and decreasing costs. A positive effect may be related to disease condition and specialty training of case managers.[42,43]

*Audit and feedback* is the provision of retrospective feedback of clinical performance to providers. It may include comparisons with other providers and/or specific recommendations for improvement. Studies have reported variable effectiveness. Audit and feedback alone modestly improves provider prescribing and test ordering behavior.[11,13–15,25,44,45]

The team can select from the above dissemination and implementation options to custom tailor a treatment strategy based on effectiveness of interventions, barriers within their organization, and resources available to the team. If the organization has not engaged in these types of activities in the past; or if there is a substantial gap between current performance and perfect performance, a multifaceted approach should be considered. Obviously many approaches are possible. The team should remember that strategies (treatments) for perceived barriers will probably require constant re-evaluation as the program is implemented and interim analyses are performed. Barriers not diagnosed early in the program may become "painfully" clear over time.

## Development and Implementation of a Hospital-Based Program to Improve Pneumococcal Vaccination Rates

In this section we discuss our approach to developing and implementing a program to improve the pneumococcal vaccination rates for our community. We will describe the first phase of this program, which has focused on identifying high-risk hospitalized patients and vaccinating them during their in-patient stay. We will present interim results and planned changes to improving adherence. We will also describe a unique intervention—multidisciplinary rounds—that effectively engages all caregivers, including house staff, in improving performance. Fortunately, we had an evidence-based opinion leader to develop and implement this program.

### Selection of Program

The leader of this project, the director of the intensive care unit and a pulmonologist, chose improved pneumococcal vaccination for multiple reasons, including:

- Personal observation in the hospital and intensive care unit found that invasive pneumococcal disease was devastating and that, despite antibiotics, it continued to cause substantial morbidity and mortality.
- Benchmarking information from the Massachusetts Peer Review Organization concluded that national, state, and local immunization practices could be substantially improved.[47]
- Baseline performance demonstrated that 8% of patients hospitalized with pneumonia at our institution had their pneumococcal vaccination status assessed and vaccination offered (Massachusetts Peer Review Organization chart review).
- The 23 capsular types in the vaccine represent at least 85% of the serotypes causing invasive disease and the 6 serotypes most frequently associated with invasive drug-resistant pneumococcal infection in the United States are represented in the vaccine.[48] The vaccine is about 69% effective in preventing invasive pneumococcal disease.[48]
- Literature noting that reactions to revaccination of patients after 4 years, although associated with more frequent local reactions, were not associated with more systemic reactions.[48]
- Two thirds of persons with serious pneumococcal disease have been hospitalized within the previous 4 years.[49]
- Reports of successful hospital-based programs showed improving pneumococcal vaccination status.[49–52]
- Predictions that if the hospital-based pneumococcal vaccination program could be leveraged to all high-risk patients in the community through improved inpatient performance and community outreach programs, 9 cases of invasive pneumococcal disease and 3 deaths could be prevented each year in our community (see Appendix 1 for calculations).

Those observations from the literature and review of our own institutional performance drove the team to develop and implement the program. This same information was used to "make the case" to community physicians, house staff, care management, and nursing that this program was worth pursuing.

### Setting Goals

The team chose perfect performance (100% adherence to the guidelines) for the in-hospital phase of the project.

### Assessment of Barriers to Adherence for the Hospital Phase

The team assessed knowledge, attitudinal, and behavioral barriers and developed specific strategies by which to overcome them. They developed a multifaceted approach to improve performance.

### Knowledge

*Lack of awareness.* The team chose to present "the case" for a hospital-based program in multiple continuing-medical-education-type settings. An expert from the Massachusetts Health Department presented at medical grand rounds. The team leader then presented at multiple medical staff meetings, reinforcing the scientific justification and encouraging active discussion of risks and benefits.

*Lack of familiarity.* Brief summaries defining candidates for vaccination or revaccination were distributed to medical staff and made available on patient charts, thus obviating the need for practitioners to remember guideline details (see Appendix 2, guideline and physician order sheet). In addition, multiple small-group interactive sessions with the medicine house staff, reviewing the science and "the case" for change, were presented. The leader addressed concerns about complications secondary to revaccination by presenting Centers for Disease Control literature.[53]

### Attitudes

*Lack of agreement with specific guideline.* Most of the issues around the pneumococcal vaccine guideline were addressed through the specific information used by the team leader to "make the case."

*Lack of agreement with guidelines in general.* This project was initiated after several highly successful guideline projects in stroke and secondary prevention in cardiovascular disease. The medical staff and house staff were therefore relatively comfortable with guidelines in general. Thus, this was not a substantial barrier.

*Lack of self-efficacy.* This was not an issue with this intervention.

*Lack of outcome expectancy.* This was addressed by "making the case" to practitioners. The more global community view was thus easier to understand.

*Lack of motivation/inertia.* This issue was addressed by developing simple implementation strategies, including pre-printed guidelines and order sheet placed in charts (Appendix 2).

### Behavior

*Guideline factors.* The simple guideline that also served as an order form (Appendix 2) was provided on each chart.

Issues regarding the ease of its availability may have been a problem (see below).

*Patient-related factors.* Patient-related factors did not appear to be a problem for this particular guideline.

*Environment-related factors.* Environment-related factors were not perceived to be a problem. The hospital was actually reimbursed separately for pneumococcal vaccine[48] and physicians' time expenditure was kept to a minimum through house staff ordering and the use of the guideline and order sheet. A reminder system focusing on the house staff was initiated through multi-disciplinary rounds (see below). We also created an immunization profile in the permanent patient registration. This made it easier to track progress and avoid inappropriate reminders to physicians and unnecessary vaccinations to patients. This system automatically notifies physicians' offices that the vaccination has been given.

### Multidisciplinary Rounds

Early in 2001 the Internal Medicine Program at Berkshire Medical Center initiated a series of 1-hour rounds 3 times per week to review all ward teaching cases and focus on key interventions. These rounds included:

1. All residents on ward rotations
2. Chair of medicine or associate director of the training program
3. Chief resident
4. Care management personnel
5. Nurse managers from all medical wards
6. Patient safety officer
7. Representative from operations

Checklists covering essentials for patients with heart disease, stroke, pneumonia, and diabetes are presented on a board and match checklists in patient charts. House staff are reminded of all essential interventions and actively discuss, with attending and chiefs, specific questions about patient eligibility or new evidence. The resident then discusses the multidisciplinary team recommendation with the attending physician. This system has lead to near perfect provision of secondary prevention strategies in patients with coronary artery disease and reinforced essential recommendations from our stroke team. Since provision of these essential noncontroversial services (eg, acetylsalicylic acid after acute myocardial infarction in eligible patients) is framed as a potential medical error of omission, the entire team is focused on assuring provision of these essential services.

The pneumococcal vaccine protocol is included in these multidisciplinary rounds, but has not been emphasized as strongly as several other interventions.

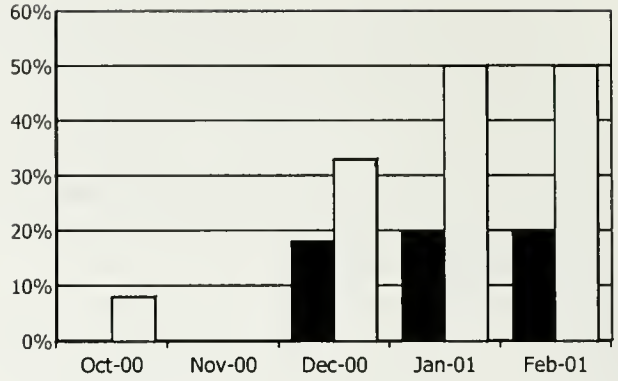


Fig. 3. In-patients receiving pneumococcal vaccine at Berkshire Medical Center. Clear bars represent total percentage of patients with pneumonia who received the vaccine. Black bars represent percentage of patients hospitalized for greater than 2 days who received the vaccination.

### Interim Results

Figure 3 shows the results to date. Now 20% of all patients over age 65 hospitalized on the medical service for over 2 days (compared to 0–1% baseline) are screened and receive vaccine if eligible. Fifty percent of all pneumonia patients (compared to 8% baseline) are screened and vaccinated if eligible.

Based on interim results that show improvement but nowhere close-to-perfect adherence to recommendations, we are considering the following interventions:

- Reemphasis of determination of pneumococcal vaccination status in all patients and administration of vaccine at multidisciplinary rounds.
- Revitalized efforts to place pneumococcal vaccine guideline and order sheet on all patient charts.
- Implementation of a more comprehensive program of identification of at-risk patients by nursing.[48]
- Nursing education emphasizing the value of the program and the case for change. Also, improve nursing familiarity with indications and benefits of vaccination, emphasizing the use of the guideline/order sheet.
- Implementation of standing orders based on increased identification of at-risk patients.[54]

### Next Steps for a Community-Based Program

Though we strive for perfect in-hospital performance, we are also beginning our community outreach programs.

Our health system includes about 900 nursing home residents, most of whom are candidates for vaccination. We are considering the use of standing orders in that population.[54]

We have an active community health presence through our "Accent on Health" program and will consider community-based programs, including reaching out to our clin-

ies, and public education programs. Such programs have been shown to result in 33% higher vaccination rates.[55]

Our provider community is now well aware of the importance of pneumococcal vaccination. Reminder systems and practice-based tracking systems can result in a 30% increase in influenza vaccination rates.[56] The use of preventive health check lists in physician offices has increased pneumococcal vaccination rates from 5% to 42%.[57]

Education of our emergency department staff and implementation of a program in that setting is under discussion.

Implementation of our new medical information system will improve the accuracy of the immunization database and communication to all caregivers. It will include concurrent electronic reminders.

## Summary

We have presented an approach to translating evidence into practice, based on identification of real opportunities, pursuit of perfect performance, identification of barriers to adherence (differential diagnosis), and strategies by which to overcome those barriers (treatment options). We have moved from the general principles in the literature to a specific program to dramatically improve pneumococcal vaccination rates in our hospital and community.

Behavioral strategies to improve practitioner performance are well researched and highly effective when properly used. A behavioral strategy integrating identification of evidence-based practitioner opinion leaders effectively engaging evidence users is likely to have a rapid and profound impact on improving performance.

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Appendix 1

## Calculation of Benefit of 100% Pneumococcal Vaccination to Eligible Adults

| Description | *n* or % |
|---|---|
| Berkshire Health Systems service area[1] | |
| Children (< 18) | 27,784 |
| Seniors (> 65) | 26,425 |
| Adult population | 96,791 |
| Adult population[2] | 96,791 |
| Estimated high risk population percentage* | 10% |
| High risk adults | 9,679 |
| Estimated vaccination rate[3] | 20% |
| Total number of eligible high risk adults | 7,743 |
| Senior population | 26,425 |
| Estimated vaccination rate in Massachusetts[4] | 53% |
| Total number of eligible senior citizens | 12,420 |
| Total opportunity to vaccinate (eligible high risk adults and seniors who have not already been vaccinated ) | 20,163 |
| Vaccination effectiveness[5] | 69% |
| Projected cases of pneumococcal bacteremia/year | |
| Rate without vaccination[6] | 0.00066 |
| Rate with vaccination = rate without × (1 – effectiveness) | 0.0002079 |
| Applied to the Berkshire Health Systems service area | |
| Cases of bacteremia at current vaccination rate | 13.3 |
| Cases of bacteremia at 100% vaccination | 4.2 |
| Cases of pneumococcal bacteremia prevented per year | 9.1 |
| Mortality rate with pneumococcal bacteremia[7] | 35% |
| Mortality at current vaccination rate | 4.7 |
| Mortality at 100% vaccination | 1.5 |
| Lives saved per year with 100% vaccination | 3.2 |

* High risk population is defined as chronic illness with cardiovascular or pulmonary disease, liver disease, alcoholism, diabetes mellitus, cerebrospinal fluid leaks, functional or anatomic asplenia, human immunodeficiency virus infection, or other immunocompromise, those persons living in long-term care facilities, and Native American populations.

1. Personal communication, Berkshire Health Systems Finance Department, 2001.
2. Centers for Disease Control. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices. MMWR 1997;46(RR-8):1-24. (Age 50-64· Prevalence of chronic pulmonary disease = 12%)
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7. Centers for Disease Control. Adult immunization programs in nontraditional settings: quality standards and guidance for program evaluation. MMWR 2000;49(RR-1);1-13. (Based on case fatality rate in elderly. Correlated with adult inner-city hospitalized patients)

Appendix 2

DOCTOR'S ORDER SHEET

Berkshire
Medical Center
Berkshire Health Systems
725 North Street, Pittsfield, MA 01201

| DATE | TIME | | TRANSCRIBER |
|---|---|---|---|
| | | **Pneumococcal Vaccine** | |

Doctor:

Has your patient had a Pneumococcal vaccine? ☐ Yes Date: ☐ No

Administer Pneumococcal vaccine ☐ Yes Dose 0.5 mL IM or SC ☐ No ☐ Patient refused vaccine

Signature: Beeper:

**This serves as a physician order**

| **Pneumococcal vaccine is recommended for:** | **Revaccination ONCE, 5 years after the first dose is indicated for:** |
|---|---|
| • All adults 65 years of age and older | • Persons > 65 years of age, if they were, < 65 years of age at the time of vaccination |
| • Persons 2-64 years of age | • Persons 2-64 years of age at highest risk of complications, or whose antibodies decline rapidly |
| • Persons who have a chronic illness such as cardiovascular or pulmonary disease (not asthma), liver disease, alcoholism, diabetes mellitus, or CSF leaks | |
| • Persons who have functional or anatomic asplenia | |
| • Persons who have HIV infection | |
| • Persons who are immunocompromised (including immunosuppression caused by medication, renal failure or nephrotic syndrome) | |
| • Persons who are living in long-term care facilities | |
| • Native American populations | |

**ALL OTHER ORDERS ARE TO BE PLACED ON ADDITIONAL DOCTOR'S ORDER SHEET**

### Discussion

**MacIntyre:** One of the things that strikes me about your talk and Gordon [Guyatt]'s earlier today is that I think evidence-based medicine enthusiasts tend to kind of polarize things—that there are evidence-based clinicians who are really doing the right thing and then there are a bunch of idiots out there who pay no attention to the evidence at all. I prefer Gordon's way of approaching it: that we really are always acting on evidence and that it just depends what the level or the strength of that particular evidence is. I think what you really mean to say is that there are some clinicians who will take it to as high a level of evidence as they can, and there are others who are still kind of hung up at some intermediate levels of evidence that guide their practice. I just think it is overly simplistic to imply that there are 2 schools of thought: evidence-based and not evidence-based.

**Ellrodt:** If it appeared that I was polarizing, then I didn't express it well. I think the idea is that there is a spectrum, and that obviously we have a lot of "evidence-based users." Look at the baseline for coronary artery disease: we're at 100%. So there are many physicians practicing evidence-based medicine out there. They weren't necessarily people who could go through and critically search and appraise. So there's a whole spectrum. If it appears that I'm polarizing it, I don't mean to be doing that at all.

**MacIntyre:** My more serious concern or problem with this whole concept is that the available evidence is rarely compelling. In intensive care units, for instance, I think most of the time the decisions must be based on evidence that is nowhere near compelling. My problem then becomes how we design management strategies under those circumstances, when high level evidence from randomized controlled trials does not exist, and lower levels of evidence must be used. We certainly should all switch to an evidence-based approach; unfortunately, the evidence foundation we're building on is still pretty thin, because compelling evidence is just not there to support a lot of what I do. And although I'd love to have randomized controlled trials for every decision I make, I'll bet that fewer than 10 or 15% of the decisions I make actually have that level of supporting evidence.

**Ellrodt:** Notice that what we went after were interventions where there is compelling evidence. We don't pursue less well supported interventions in the same way. So we don't go through and say "This is the way to wean and we expect 100% adherence to this recommendation." Since there isn't compelling evidence, we expect give-and-take and a prominent role for clinical judgment. So when you look at performance, for example, around certain types of guidelines, 50–60% adherence may be excellent. I'll give you an example: we have done a lot of work on guidelines aimed at helping to decide who is ready to be discharged. For example, one was which patients is it safe to send home after upper gastrointestinal bleed? At what point? You could make an argument to shoot for 100% on that—that all patients who are eligible should go home. But that's exactly what you don't want. So you can make an argument for that kind of thing where there's clearly an awful lot of risk in a guideline that's not perfect and not clear. Adherence in that case maybe should be 60 or 70%, and that's it.

We studied that in a report[1] in which we asked why certain patients were not sent home according to guideline recommendations. When we went through the charts we said, "Thank God they weren't sent home! Thank God somebody was thinking!" So the reason I kept saying "compelling evidence" was because I think that, for these particular interventions that we've picked out, there is compelling evidence and you should be doing it in eligible patients. But for other things, a lot of other things—and, unfortunately, for a lot of what we do in the intensive care unit—there is not that compelling evidence. So, therefore, far more constrained enthusiasm for doing it one way or another needs to be in place. Does that address your concerns?

#### REFERENCE

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**MacIntyre:** In fact, it underscores my concerns. We have developed guidelines for mechanical ventilation that are based in large part on the ARDS [acute respiratory distress syndrome] Network study,[1] which indicated that tidal volume of 6 mL/kg is better than 12 mL/kg. That's all it says. Out of hundreds of possible settings, they could have studied, the ARDS Network researchers chose two and found that one is better than the other. Does that mean that we ought to interpret this evidence as saying that 12 mL/kg is bad and any tidal volume lower than that is good? Or is 6 mL/kg good and everything above that bad? When you have only those 2 points on a huge continuum and then try to come up with guidelines to follow in practice, considerable other inputs (lower levels of evidence) must be called into play. We want to base practice on the highest level of evidence, but the evidence, unfortunately, is just that 6 mL/kg is better than 12 mL/kg, so we have to throw in a fair amount of animal data, clinical observations, nursing observations, therapist skills, and a whole bunch of other stuff, and somehow try to make some clinically meaningful guidelines out of that evidence base.

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for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18):1301–1308.

**Guyatt:** Why are you bothering to try to standardize when you don't know what you're doing?

**MacIntyre:** I think what I'm doing is trying to get a practice set up in my institution whereby people will not use tidal volumes that harm patients. I think you would agree that the evidence—if you take it from the animals all the way to humans—is that high tidal volumes are bad in patients with stiff lung problems such as ARDS and that coming up with a set of guidelines as to how to operate the ventilator to prevent that from occurring would seem reasonable. In the early 1990s the American Thoracic Society and the Society of Critical Care Medicine both did surveys on common practice guidelines, and the average tidal volume in both of those groups, among a large number of intensivists, was up around 12 mL/kg. That is why the ARDS Network chose that as the "control" tidal volume. And the 6 mL/kg value, by the way, was chosen because it is half of that. The study was positive. Do you not think it's now our responsibility to try to promulgate the concept that smaller tidal volumes ought to be used?

**Guyatt:** Maybe I misunderstood. You said that there were hundreds of settings, of which you know that there's evidence about one. I thought you said you were trying to standardize all the others.

**MacIntyre:** I'm sorry. I must not have phrased it properly. What I'm trying to say is we've got this piece of information that goes along with our physiologic understanding. And now the problem is how to operationalize it. You've got an important concept to guide therapy, but you have to come out with a set of ways of doing things to actually care for patients. Because the high-level evidence is usually pretty scanty and you've got to use a lot of low-level evidence (I hate to use the words *experience* and *observations*) to make it operational. You've got to have a starting tidal volume for somebody on a ventilator. You've got to select an inspiratory time. You've got to select a positive end-expiratory pressure. You have to do that to make the ventilator work. And we have precious little high-level evidence to guide us in how to do that, other than the fact that a smaller tidal volume is better than a larger one.

**Guyatt:** Well, I'm still not absolutely sure I understand you, but if on the one hand these are ways of implementing a recommendation based on a randomized trial that shows a decreased mortality, then that is one thing. It is another thing that what people tend to do is think we need guidelines for everything—for all aspects of care. And what I think Gray [Ellrodt] is doing, which strikes me as superb, is to say, "Let's identify the areas where we really know what we're doing and try to change behavior in those areas."

As for the rest of our practice, a strong argument can be made for not bothering to try to standardize behavior, because the behavior we're trying to standardize—we may subsequently find out we were getting everybody to do the wrong thing. It takes a lot of time and energy to standardize behavior. Perhaps we should restrict that to areas where we really have strong evidence. And where we don't have strong evidence, let the heterogeneity of practice continue. In fact, that labels for us the areas where we need to adduce new and strong evidence, so then that would support the approach that Gray is taking.

**MacIntyre:** If the evidence is clear and compelling, I think we all agree. And if we have precious little or no data, we all agree to let the heterogeneity of practice remain. I'm concerned about the gray area in the middle, where there is some evidence (some of it stronger than others) suggesting that we ought to be doing things a bit differently. And I think tidal volume is a pretty decent example: we ought to be using small tidal volumes. I'm trying to determine how to operationalize that. Maybe "guidelines" is a bad word, but we should at least come up with a philosophical approach (I'll be very vague there) or some kind of *operational mindset* as to how we're going to operate a ventilator that will keep the tidal volume on the small side.

I have difficulty with how to do that. I think that when high-level evidence exists, the focus ought to be on changing clinicians' behavior to employ the proven strategy. Conversely, when little or no high-level evidence exists, I have no problem with letting people do what they want. It's the situation in the middle that I am having difficulty with: where there is some good evidence but it's not so complete that you've got the whole package and can mandate what should be done.

In developing guidelines for the American College of Chest Physicians, the ACCP, and the American Association for Respiratory Care we ran into similar problems. There are some really compelling studies about certain things we ought to do to improve the ventilation withdrawal process, but there were also many gaps in the high-level evidence base, and we had to resort to lower levels of evidence, including our observations and experience, to come up with something reasonable to make it operational for 2001.

**Ellrodt:** Part of evidence-based medicine, I think, is knowing what you know and knowing what you don't know, and identifying them—saying, "We're pretty clear on this, we're vague on this, and we are clueless on this"—and just admitting it up front. Especially when you're talking to practitioners you're saying, "Look, we're trying to move forward; we believe that there's pretty good evidence for 6 mL/kg tidal volume—for that one

piece of ventilator management in ARDS." There are all these other pieces that we're not so sure of. Can we come to some consensus around this piece of evidence, and we're going to fill in a few of the blanks based on weaker evidence. Can we have agreement on that, or in what situations can we have some flexibility on that? But let's all agree that we're going to try to get to 6 mL/kg. Does that make sense?

**MacIntyre:** Yes, but can I just use another example? As you know, the activated protein C (APC) trial[1] has shown that the drug is beneficial in sepsis, but it is going to be expensive. Pharmacy and therapeutics committees are going to have to wrestle with who's going to get that drug and who isn't. And the question is going to come up: should you have hard and fast rules that follow only the inclusion and exclusion criteria of the trial? Or are you allowed to use your experience to widen the applications? Or are you going to go into some of the subgroup analysis to find reasons to perhaps restrict the applications? Do we take the available data and rigidly apply it? Or do we integrate it with lower-level evidence to develop a different operational plan?


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**Ellrodt:** I think you've hit on the process. Remember, at the top of the whole guideline hierarchy was local consensus around the evidence. You need to build consensus as to what you're going to do and how you're going to do it. Consensus really helps in those areas that are vague or gray. You need to have some consensus around the interpretation, and some consensus around which you're going to be flexible. And you may want to set up a system that allows that.

You set up a system where, for example, every patient who really fits all the inclusion and exclusion criteria gets APC. Those patients get the drug: just to check it off and somebody in the pharmacy takes a look at it. Then there's a whole group of patients who are borderline. What you may want to do is flag those because you don't know, and say, "We need to discuss this." There may be an expert from the committee who goes through those with the practitioner, saying, "Let's talk over why this patient may or may not benefit." Not everybody who is giving APC is going to know all the details of the study. But hopefully a few people really understand the subtleties of it. So one group of patients automatically get it, another group receives consultation, and another group are really going to have to fight to get it. You can set up different ways to do it, based on how solid the evidence is. There are ways to handle this, but it's clear that for APC you're never going to get to the point where 100% of the patients who have sepsis get APC. You're not going to go for that. That would be an inappropriate goal.

**Rowe:** Regarding implementation of guidelines: how much do you think the success of a particular guideline depends on what you call charisma, versus just observation—the Hawthorne effect[1] of knowing that your work is being scrutinized by the Chief of Medicine or other leaders in the field? It doesn't need to be the Chief of Medicine; it could it be a nurse who's reporting to an administrator. How much of it is the charismatic leadership and how much of it is the observation—that people know they're being watched?


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**Ellrodt:** Well, I might put observation instead of concurrent feedback. If somebody's looking through my chart, that's concurrent feedback as to what I should be doing. So maybe it's under that model: here comes the case manager coming through and you say I know, I mean our people know darn well what they're going to be looking for. They're trained to know what they're looking for. Then that's the concurrent reminder: "Oh, yeah, here comes the case manager. Hmmm, you know, I didn't order aspirin for this patient; I'd better go do it." That's one way.

As for charismatic leadership, I'm talking about for the whole program, not just for those individual kinds of things. I'm talking about someone who can go out there and say, "Look, we're going to hit 100% on these 5 key interventions after acute myocardial infarction. And I'm going to drive you there." You can call it charisma or whatever you want, but we're going to get there. I'm going to take accountability for getting there. OK? So for each one of our projects, there's someone who says, "This is my job." For secondary prevention, that's my job. For pneumococcal vaccination, that's Dan Doyle's job, the head of the ICU. Everybody has someone who is high up in our place who's leading every one of those, and they have attached to them, right at the hip, by the way, the house officer, usually a chief resident, and another house officer, who are held accountable for doing this. You want to do this project? You're going to be accountable for it. And you pick the people very carefully. I actually go through and pick who's going to lead each one of these. I know who the people are who are, first of all, credible. I have my own internal way of picking out opinion leaders, and I add to it the evidence-based practitioners and opinion leaders: and therefore they lead the project. I think it's very important. If you don't have that leadership, it's going to fall apart; it's never going to make it—I think.

# The Evidence for Secretion Clearance Techniques

Dean R Hess PhD RRT FAARC

**Introduction**
**Definition of Techniques**
**Narrative Reviews**
**Systematic Reviews**
**Comprehensive Review**
  **Chest Physiotherapy**
  **Autogenic Drainage and Active Cycle of Breathing Technique**
  **Positive Expiratory Pressure**
  **Flutter Therapy**
  **High Frequency Chest Compression**
  **Intrapulmonary Percussive Ventilation**
  **Manual Hyperinflation**
  **Mechanical In-Exsufflation**
**Observations and Limitations of this Review**
**Lack of Evidence Versus Lack of Benefit**
**Summary**

**Many acute and chronic respiratory diseases are associated with increased respiratory secretions in the airways. Narrative reviews and a few systematic reviews of secretion clearance techniques have been published. These reviews raise concerns regarding the lack of evidence to support the various secretion clearance techniques. I conducted a comprehensive MEDLINE search of the following subjects: chest physical therapy, chest physiotherapy, postural drainage, forced expiratory technique, autogenic drainage, high-frequency chest wall compression, flutter device and secretions, positive expiratory pressure and secretions, intrapulmonary percussion, mechanical in-exsufflation and secretions. This was followed by a comprehensive search of cross-references to identify additional studies. The results of this review are reported herein. There are a number of methodological limitations of the literature reporting studies of the use of secretion clearance techniques. Most of the studies were small, most used crossover designs, and few used sham therapy. Many studies were limited to short-term outcomes such as sputum clearance with a single treatment session. Despite the clinical observation that retained secretions are detrimental to respiratory function and despite anecdotal associations between secretion clearance and improvements in respiratory function, there is a dearth of high-level evidence to support any secretion clearance technique.** *Key words: secretion clearance, respiratory secretions, evidence-based medicine.* [Respir Care 2001:46(11):1276–1292]

## Introduction

Healthy lungs effectively clear mucus from the airways via the mucociliary escalator. When the mucociliary escalator is challenged (for example, with infection or aspiration), effective secretion clearance is provided by the cough reflex. Many acute and chronic respiratory diseases are

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A version of this paper was presented by Dr. Hess during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20-22, 2001, Banff, Alberta, Canada.

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associated with increased respiratory secretions in the airways due to increased mucus production, impaired mucociliary transport, or a weak cough. It is generally assumed that retained secretions promote infection, atelectasis, and abnormalities in gas exchange and lung mechanics. All respiratory therapists have had experiences in which secretion clearance improved respiratory mechanics and gas exchange.

In patients with chronic respiratory diseases associated with mucus expectoration (for example, cystic fibrosis, chronic bronchitis, and bronchiectasis), it is unknown whether increased respiratory secretions contribute to the deterioration of respiratory function or whether this is merely a symptom associated with the progression of the disease. Moreover, it should be recognized that increased expectoration of mucus does not imply mucus stasis in the airways of the lungs. There is a relative lack of evidence describing the effect of increased respiratory tract secretions on the progression of disease, and there is even less evidence that secretion clearance techniques improve the course of disease. Despite this lack of evidence, as clinicians we are troubled by respiratory secretions and standard practice calls for efforts to clear these from the lungs. Indeed, an important proportion of respiratory therapists' time is spent in efforts to evacuate secretions from the lower respiratory tract. Moreover, in recent years a variety of equipment (of varying cost) has become available to assist with this.

## Definition of Techniques

Many techniques can be used to improve secretion clearance from the lower respiratory tract (Table 1). Those that are considered in this review are defined below.

Table 1. Techniques Used to Clear Secretions from the Lower Respiratory Tract

| |
|---|
| Directed cough |
| Forced expiratory technique |
| Chest physiotherapy (posture drainage, percussion, and vibration) |
| Positive expiratory pressure |
| Flutter |
| Active cycle of breathing |
| Manual hyperinflation |
| Autogenic drainage |
| High frequency chest wall oscillation |
| Intrapulmonary percussive ventilation |
| Mechanical in-exsufflation |
| Exercise* |
| Suctioning* |
| Bronchoscopy* |
| Mucus-modifying medications* |

*Not considered in this review

*Directed cough.* A technique that mimics the attributes of an effective spontaneous cough; the cough can be manually assisted by application of external pressure to the epigastric region or thoracic cage during the expiratory phase (as in the patient with neuromuscular disease); sometimes called quad coughing.

*Forced expiratory technique* (FET). Sometimes called huff coughing, this technique consists of one or 2 huffs from mid-to-low lung volumes with the glottis open, followed by relaxed diaphragmatic breathing.

*Chest physiotherapy* (CPT). This technique has traditionally included postural drainage, percussion, and vibration. Postural drainage is a technique in which the patient is positioned to facilitate gravity drainage of secretions from the airways. Percussion is a technique of clapping the chest wall. Vibration applies fine shaking of the chest wall, usually during the expiratory phase. Percussion and vibration can be applied using either manual or mechanical techniques.

*Positive expiratory pressure* (PEP). With this technique, the patient exhales against a pressure of 10–20 cm $H_2O$.

*Flutter.* This technique uses a device that produces PEP with oscillations in the airway during the expiratory phase.

*Active cycle of breathing.* This technique includes breathing control, FET, thoracic expansion techniques, and may include CPT.

*Manual hyperinflation.* This is a technique to improve secretion clearance by use of a manual ventilation device (manual resuscitator). It can be used in conjunction with CPT and manually assisted cough. It involves a slow deep inspiration with a manual ventilation device, an end-inspiratory pause, and a fast, unobstructed exhalation.

*Autogenic drainage.* This is a 3-level breathing sequence beginning at low lung volumes, followed by breathing at mid-lung volumes, followed by deep breathing and huff coughing.

*High-frequency chest wall oscillation.* This techniques uses an inflatable vest that attaches by hoses to an air-pulse generator producing pressures to about 50 cm $H_2O$ at frequencies of 5–25 Hz.

*Intrapulmonary percussive ventilation.* This technique uses a pneumatic, oscillating pressure device that generates oscillations in the range of 100–300/min at pressures of 5–35 cm $H_2O$.

*Mechanical in-exsufflation.* Application of a high pressure to the airway (20–30 cm $H_2O$) followed by rapid reversal of pressure (–30 to –40 cm $H_2O$) to simulate cough.

## Narrative Reviews

Many narrative reviews of secretion clearance techniques have been published,[1-16] including a series of reviews in the *European Respiratory Journal*.[17-22] There have also

been several clinical practice guidelines on some secretion clearance techniques published by the American Association for Respiratory Care.[23–25] Appreciating the potential biases of a narrative review, it is interesting to note that many of these reviewers raise concerns regarding the lack of evidence to support the various secretion clearance techniques—this in spite of the general enthusiasm by clinicians for these procedures. A few of these concerns are highlighted below.

> Although physiotherapy is seen as an integral part of most multidisciplinary intensive care units, there is only limited evidence concerning the effectiveness of physiotherapy in this setting.[1]

> The literature concerning CPT and its effect on the pulmonary function of cystic fibrosis patients is extensive and inconsistent in its findings.[2]

> In mechanically ventilated children, chest physiotherapy cannot be regarded as a standard treatment modality.[3]

> . . . we conclude that mechanical percussion of the chest as applied by physical/respiratory therapists is ineffective and perhaps even detrimental in the treatment of patients with acute exacerbations of chronic obstructive pulmonary disease.[4]

> The acute effect of postural drainage and percussion on pulmonary function has been studied repeatedly, with equivocal results.[10]

> Much research is needed before optimal techniques and procedures for secretion clearance in intensive care unit patients can emerge.[14]

> This paper, like many others, demonstrates that the evidence to indicate to either patients or health professionals which airway clearance technique they should be using is not available.[20]

> There continues to be widespread debate as to which airway clearance regimen should be used and when.[20]

### Systematic Reviews

Several systematic reviews of secretion clearance techniques have been published. Thomas et al[26] conducted a meta-analysis of CPT management of cystic fibrosis (CF) patients. Specifically, they examined PEP, FET, exercise, autogenic drainage, and standard CPT. Their results are summarized in Table 2. They concluded that standard CPT resulted in significantly greater sputum expectoration than no treatment. It is important to note, however, that they based this finding on p value analysis and not on the quantity of sputum produced. They also found that the combination of standard CPT and exercise was associated with a moderate increase in forced expiratory volume in the first second ($FEV_1$), compared to standard CPT alone. No other differences between CPT modalities were found.

Jones and Rowe[27] reported a systematic review of bronchopulmonary hygiene physical therapy in bronchiectasis and chronic obstructive pulmonary disease. They identified 7 studies that met their criteria for review, which included a total of 126 patients. Because of the small sample sizes in those studies, the low quality of the studies, and the mixed results of the trials, they concluded that there was insufficient evidence to support or refute administration of bronchopulmonary hygiene physical therapy for those patient groups.

Thomas et al[28] conducted a systematic review of mechanical vibration for clearing of bronchial secretions. They reviewed the literature for this technique as applied to both chronic obstructive pulmonary disease patients (3 trials) and cystic fibrosis (CF) patients (6 trials). They found that the studies were generally of poor methodological quality. They concluded that the existing clinical trial data are inconclusive and, therefore, that the clinical use of mechanical vibrators cannot be scientifically supported.

Several systematic reviews of this topic are available in the Cochrane Database. One of these[29] is essentially the same analysis as that reported above.[27] van der Schans et al[30] conducted a Cochrane review comparing CPT to no CPT for CF. They were unable to identify any studies that addressed this question in a meaningful manner, and concluded that no clear evidence to date supports the beneficial effects of CPT in CF patients. However, they[30] did report that short-term crossover trials (excluded from this review because of poor methodological quality) suggest that CPT could have beneficial effects in CF patients. A follow-up review, not yet reported, is underway to evaluate conventional CPT compared to any form of CPT in CF patients.[31]

Flenady and Gray[32] conducted a Cochrane review on the use of CPT for preventing morbidity in babies being extubated from mechanical ventilation. They reported that CPT was not associated with a reduction in postextubation lobar collapse, although a reduction in reintubation was associated with the use of CPT. Because of the small number of patients studied, they concluded that there are not enough data to assess the safety of CPT for babies receiving mechanical ventilation.

### Comprehensive Review

I conducted a MEDLINE search using Internet Grateful Med for the following subjects: chest physical therapy, chest physiotherapy, postural drainage, forced expiratory technique, autogenic drainage, high-frequency chest wall compression, flutter device and secretions, positive expi-

Table 2. Results of a Meta-Analysis of Chest Physiotherapy Modalities in Cystic Fibrosis

| Comparison | Outcome Measure | Studies (*n*) | Effect Size (SD units)* | 95% CI | Effect Size (natural units) | p |
|---|---|---|---|---|---|---|
| Standard CPT versus control | p value analysis | 3 | 0.61 (favoring CPT) | — | 7.5 g sputum | < 0.001 |
| Standard CPT versus PEP | sputum | 6 | 0.082 (favoring PEP) | −0.39 to 0.23 | 2 g sputum | 0.30 |
| | $FEV_1$ | 6 | 0.023 (favoring PEP) | −0.32 to 0.43 | 4 mL $FEV_1$ | 0.27 |
| Standard CPT versus CPT + exercise | $FEV_1$ | 3 | 0.48 (favoring CPT + exercise) | 0.07 to 1.02 | 6.4% of predicted $FEV_1$ | 0.04 |
| Standard CPT versus FET | sputum | 4 | 0.27 (favoring FET) | −0.65 to 0.10 | 3.3 g sputum | 0.08 |
| | $FEV_1$ | 5 | 0.13 (favoring standard CPT) | −0.17 to 0.43 | 0.07% of predicted $FEV_1$ | 0.19 |
| Standard CPT versus cough | sputum | 2 | 0.23 (favoring standard CPT) | 0.49 to 0.95 | 4.5 g sputum | 0.27 |
| Manual versus mechanical percussion and vibration | sputum | 4 | 0.12 (favoring manual) | −0.35 to 0.58 | 1 g sputum | 0.31 |
| | $FEV_1$ | 3 | 0.04 (favoring mechanical) | −0.54 to 0.47 | 0% of predicted $FEV_1$ | 0.44 |

*Effect size is calculated by dividing the mean difference in outcome between the 2 groups by the pooled SD of the 2 groups. An effect size of 0.2 SD units represents a small effect, 0.5 a medium effect, and 0.8 a large effect.
CI = confidence interval
CPT = chest physical therapy
PEP = positive expiratory pressure.
$FEV_1$ = forced expiratory volume in the first second
FET = forced expiratory technique
(Adapted from Reference 28.)

ratory pressure and secretions, intrapulmonary percussion, mechanical in-exsufflation and secretions. The search was limited to the English language, all study groups, all age groups, all publication types, all gender, all journals, 1966 to 2000. This was followed by a comprehensive search of cross-references to identify additional studies. The results of this review are reported below.

## Chest Physiotherapy

The literature search for *chest physiotherapy* resulted in 34 studies with useable data. The remaining citations were reviews, did not include useable data (for example, only included mean data),[33–38] were not germane to the subject (for example, postoperative breathing exercises),[39–46] or presented the results in a manner that was not amenable to quantitative review.[47–62]

The effect of CPT on sputum mass was reported in 12 studies (Table 3).[63–73] Several observations can be made from these studies. The studies were of short duration: none exceeded 5 weeks. The number of patients included in the studies was small. In all of the studies but two, a crossover design was used. Thus, the methodological quality of the studies was poor. The increase in sputum produced with CPT was generally small and the 95% confidence interval (CI) included zero (no effect) in six of the trials. Although the possibility of improved secretion clearance cannot be excluded based on these studies, this evidence does not strongly support a treatment benefit from improved secretion clearance with CPT.

The effect of percussion was reported in 10 studies (Table 4).[74–79] These studies were also of short duration and all used a crossover design. In every trial but one, the 95% CI included zero (no effect). Because of the poor methodological quality of these studies and the failure of most to report a treatment benefit, it is concluded that there is insufficient evidence to support a benefit from the use of percussion as a technique to improve secretion clearance. Moreover, there is no benefit from the use of mechanical percussion versus manual percussion.

Sutton et al[80] studied the effect of percussion and vibration on the clearance of a radioactive aerosol from the lungs and reported that these techniques did not enhance tracheobronchial clearance.

Holody and Goldberg[81] studied the effect of mechanical chest wall vibration on arterial partial pressure of oxygen ($P_{aO_2}$) in 10 patients with atelectasis or pneumonia (8 mechanically ventilated). They reported an improvement in $P_{aO_2}$ with this technique, but it was small (mean of 10 mm Hg) and there was no control.

The effect of CPT on $FEV_1$ was reported in 8 studies (Table 5).[71,73,82–85] These were short-term studies and only 2 of them were prospective randomized trials. The treat-

Table 3. Summary of Studies that Evaluated the Effect of Chest Physiotherapy on Mass of Sputum Produced

| First Author | Year | Duration | Diagnosis | *n* | Intervention | Control | Design | Difference (g) | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| Lorin[64] | 1971 | 1 tx | CF | 17 | PD | cough | crossover | 1.6 | 0.6 to 2.6 |
| Etches[65] | 1978 | 21 tx | RDS | 6 | CPT | suction | crossover | 0.3 | 0 to 0.6 |
| Newton[66] | 1978 | 3 d | bronchitis | 79 | CPT/IPPB | no therapy | prospective randomized | 4.6 | −2.7 to 11.9 |
| May[67] | 1979 | 1 tx | bronchitis | 35 | PD/percussion | heat lamp | crossover | 4.1 | 2.2 to 6.0 |
| Bateman[68] | 1979 | 1 tx | bronchitis, bronchiectasis | 10 | CPT | cough | crossover | 10 | 4.1 to 15.9 |
| Bateman[69] | 1981 | 1 tx | bronchitis, bronchiectasis | 6 | CPT | cough | crossover | 8 | −3.2 to 19.2 |
| Sutton[70] | 1983 | 1 tx | bronchiectasis, CF, asthma | 10 | FET/PD | FET | crossover | 10 | 5.3 to 14.7 |
| de Boeck[71] | 1984 | 1 tx | CF | 9 | PD/percussion | cough | crossover | 1.3 | −4.8 to 7.4 |
| Verboon[72] | 1986 | 4 wk | CF | 8 | FET/PD during sleep | FET | crossover | 9.4 | −30.2 to 49.0 |
| Verboon[72] | 1986 | 5 wk | CF | 8 | FET/PD | FET | crossover | 0 | −11.8 to 11.8 |
| Bain[73] | 1988 | 2 wk | CF | 20 | PD | cough | prospective randomized | −0.7 | −17.8 to 16.4 |
| Steven[63] | 1992 | 1 d | CF | 24 | PD/ACB/cough | seated/ACB/cough | crossover | 9 | 4.6 to 13.4 |

CI = confidence interval
tx = treatment.
CF = cystic fibrosis.
PD = postural drainage
RDS = respiratory distress syndrome
CPT = chest physiotherapy.
IPPB = intermittent positive pressure ventilation
FET = forced expiratory technique
ACB = active cycle of breathing.

ment effect was small in all cases and the 95% CI included zero (no effect) in 6 of the 8 studies. In addition to these studies, Asher et al[86] studied the lung volumes and expiratory flows of 38 children with pediatric asthma randomized to receive CPT or placebo visits by a hospital volunteer. They reported that CPT did not improve lung function in these patients. Kerrebijn et al studied the immediate effect of CPT on pulmonary flows and volumes and reported no significant effect.[87]

Clearance of a radioactive aerosol deposited in the lungs was used to assess CPT in 7 studies (Table 6).[69,70,88–92] Although the sample sizes are small, a treatment benefit from CPT was reported in 5 studies of sufficient magnitude that the 95% CI does not include zero. It is of interest to note that the study that evaluated the effects of percussion in addition to postural drainage did not report a treatment benefit from the use of percussion.

Five prospective randomized trials studied the effect of CPT on the incidence of atelectasis (Table 7).[93–97] Three of these studies evaluated neonates after extubation and two of the studies evaluated postoperative patients. Of interest is the observation that only 1 study reported an improvement in the incidence of atelectasis with the use of CPT.

Three prospective randomized trials studied the effect of CPT on hospital length of stay (Table 8).[66,98,99] None of these reported a benefit from CPT. The study by Alexander et al[99] deserves further comment. In that study, 177 patient orders for CPT were reviewed and 105 of them were deemed inappropriate based on the authors' criteria for patients who might benefit from this therapy. Patients whose orders were deemed inappropriate were randomized to either have the CPT continued or to have it discontinued. There was no increase in mortality rate or hospital length of stay associated with the discontinuation of CPT, but there were significant cost savings associated with this intervention.

The following observations are made relative to the evidence for CPT. Most of the studies use physiologic end points such as sputum clearance, pulmonary function test results, and radioactive isotope clearance. Sample sizes are generally small, increasing the risk of statistical error. Few of the studies are prospective randomized trials; most use a crossover design. Most are short-term studies; many evaluated only a single treatment session. Only 1 study reported long-term (3 yr) effects of CPT in CF patients

Table 4 Studies Assessing the Effect of Chest Percussion on Sputum Mass

| First Author | Year | Duration | Diagnosis | *n* | Intervention | Control | Design | Difference (g) | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| Denton[5] | 1962 | 1 tx | CF | 23 | PD/mechanical percussion | PD | crossover | 11.16 | 7.3 to 15.1 |
| Maxwell[76] | 1979 | 1 tx | CF | 10 | mechanical percussor | mechanical percussion | crossover | 0.8 | −9.8 to 8.3 |
| Pryor[7] | 1979 | 1 d | CF | 16 | manual percussion/ PD | FET/PD | crossover | −17.5 | −21.9 to 13.1 |
| Murphy[78] | 1983 | 36 tx | CF | 2 | mechanical percussor | unassisted PD | crossover | −4.55 | 16.8 to 7.7 |
| Murphy[78] | 1983 | 37 tx | CF | 2 | manual percussion | unassisted PD | crossover | 6.06 | −18.1 to 6 |
| Murphy[78] | 1983 | 38 tx | CF | 2 | mechanical percussor | manual percussion | crossover | 1.51 | −11.5 to 14.5 |
| Brown[79] | 1987 | 1 tx | COPD | 24 | mechanical vibration | positioning | crossover | 1.4 | 1.8 to 4.6 |
| Gallon[74] | 1990 | 1 wk | bronchiectasis | 10 | PD/FET/fast manual percussion | PD/FET/no percussion | crossover | 3.1 | −6.9 to 13.1 |
| Gallon[74] | 1991 | 1 wk | bronchiectasis | 10 | PD/FET/slow manual percussion | PD/FET/no percussion | crossover | 4.7 | −5.9 to 15.3 |
| Gallon[74] | 1991 | 1 wk | bronchiectasis | 10 | PD/FET/fast manual percussion | PD/FET/slow manual percussion | crossover | −1.6 | −11.9 to 8.7 |

CI = confidence interval
tx = treatment
CF = cystic fibrosis
PD = postural drainage
FET = forced expiratory technique
COPD = chronic obstructive pulmonary disease

($n$ =63).[85] That study reported similar hospitalizations and hospital days for FET and CPT, no significant difference in decline in forced expiratory volume in the first second for FET and CPT, and a rate of decline in $FEF_{25-75\%}$ (forced expiratory flow in the middle half of the forced vital capacity) greater for FET than CPT.

Table 5. Studies Assessing the Effect of Chest Physiotherapy on $FEV_1$

| First Author | Year | Duration | Diagnosis | Intervention | Control | Design | *n* | Difference (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| Feldman[82] | 1979 | 1 tx | CF | PD | | B/A | 9 | 8.8 | 3.5 to 14 |
| Feldman[82] | 1979 | 2 tx | bronchitis | PD | | B/A | 10 | 0.8 | −13.5 to 11.4 |
| May[67] | 1979 | 1 tx | bronchitis | PD | heat lamp | crossover | 35 | 1.7 | −2.7 to 6.1 |
| Desmond[83] | 1983 | 3 wk | CF | PD | control | crossover | 10 | 7.1 | 2.5 to 11.7 |
| de Boeck[71] | 1984 | 1 tx | CF | CPT | cough | crossover | 9 | 2.9 | −12.6 to 18.4 |
| Mohsenifar[84] | 1985 | 1 tx | COPD | PD/manual percussor | | B/A | 10 | −1 | −8 to 6 |
| Reisman[85] | 1988 | 3 yr | CF | CPT | FET | prospective randomized | 63 | 2.8 | −0.4 to 6 |
| Bain[73] | 1988 | 2 wk | CF | PD/P | cough | prospective randomized | 20 | −0.8 | −24.4 to 22.8 |

$FEV_1$ = forced expiratory volume in the first second
CI = confidence interval
CF = cystic fibrosis.
PD = postural drainage
B/A = before and after
CPT = chest physical therapy
FET = forced expiratory technique
COPD = chronic obstructive pulmonary disease
P = percussion

Table 6. Studies Assessing the Effect of Chest Physiotherapy on Radioactive Aerosol Clearance from the Lungs

| First Author | Year | Diagnosis | Intervention | Control | *n* | Difference (%) | 95% CI |
|---|---|---|---|---|---|---|---|
| Oldenburg[88] | 1979 | bronchitis | PD | cough | 8 | −48.2 | −62.4 to −33.9 |
| Bateman[69] | 1981 | bronchitis, bronchiectasis | CPT | cough | 6 | 20.5 | 12.9 to 28.1 |
| Rossman[89] | 1982 | CF | PD | cough | 6 | 3.7 | −14.3 to 21.7 |
| Rossman[89] | 1982 | CF | PD/P | cough | 6 | 2.1 | −16.3 to 20.5 |
| Rossman[89] | 1982 | CF | PD/P | PD | 6 | −1.6 | −18.7 to 15.5 |
| Sutton[70] | 1983 | bronchiectasis, CF, asthma | FET | no therapy | 10 | 13 | 8.6 to 17.4 |
| Sutton[70] | 1983 | bronchiectasis, CF, asthma | FET/PD | no therapy | 10 | 16 | 11.6 to 20.4 |
| Sutton[70] | 1983 | bronchiectasis, CF, asthma | FET/PD | FET | 10 | 3 | −1.4 to 7.4 |
| van der Schans[92] | 1986 | COPD | percussion | PD/P | 9 | −35 | −48.9 to −21.1 |
| van der Schans[92] | 1986 | COPD | PD/P | PD | 9 | −10 | −31.9 to 11.9 |
| van der Schans[92] | 1986 | COPD | percussion | PD | 9 | −45 | −66.9 to −23.1 |
| Olseni[90] | 1994 | bronchitis | PD/FET | no therapy | 14 | 30 | 15.9 to 44.1 |
| Hasani[91] | 1994 | COPD, bronchiectasis | FET | no therapy | 19 | 26 | 23.4 to 28.6 |

CI = confidence interval
PD = postural drainage.
CPT = chest physiotherapy
CF = cystic fibrosis.
PD/P = postural drainage and percussion.
COPD = chronic obstructive pulmonary disease
FET = forced expiratory technique

CPT is not necessarily a benign therapy. There are numerous reports of adverse effects with the application of CPT. These include hypoxemia,[34,100] increased oxygen consumption,[101–106] gastroesophageal reflux in infants,[107–110] increased intracranial pressure,[111,112] Grade III/IV intracranial hemorrhage in pre-term infants,[113] encephaloclastic porencephaly (brain injury similar to that occurring with nonaccidental shaking injury in low-birthweight infants),[114] and rib fractures.[115] When a decision is made to use CPT, the potential for these adverse effects must be considered.

Based on this review, I make the following recommendations regarding the use of CPT.

1. There is no role for routine use of CPT in hospitalized patients.

2. The effect of CPT on long-term outcomes and quality of life in patients with chronic diseases such as CF is unknown.

3. There is little evidence of benefit from chest percussion and vibration, compared to postural drainage alone.

4. The evidence for improved secretion clearance with postural drainage is weak; there is insufficient evidence to support or not support the use of this therapy.

5. CPT has the potential to harm some patients under some conditions.

Table 7. Studies Assessing the Effect of Chest Physiotherapy on the Incidence of Atelectasis

| First Author | Year | Diagnosis | Intervention | Control | Design | *n* | Difference (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Finer[93] | 1979 | RDS, post-extubation | CPT | no therapy | prospective randomized | 42 | 0.38 | 0.17 to 0.59 |
| Reines[94] | 1982 | post-operative | CPT | no therapy | prospective randomized | 44 | −0.36 | −0.64 to −0.08 |
| Torrington[95] | 1984 | post-operative | CPT | no therapy | prospective randomized | 49 | −0.013 | −0.28 to 0.25 |
| Al-Alaiyan[97] | 1996 | RDS, post-extubation | CPT | no therapy | prospective randomized | 42 | −0.142 | −0.38 to 0.09 |
| Bloomfield[96] | 1998 | RDS, post-extubation | CPT | no therapy | prospective randomized | 297 | −0.03 | −0.12 to 0.06 |

CI = confidence interval
RDS = respiratory distress syndrome
CPT = chest physiotherapy

Table 8. Studies Assessing the Effect of Chest Physiotherapy on Hospital Length of Stay

| First Author | Year | Diagnosis | Intervention | Control | Design | *n* | Difference (days) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newton[96] | 1978 | bronchitis | CPT/IPPB | no therapy | prospective randomized | 27 | −0.5 | −1.9 to 0.9 |
| Graham[98] | 1978 | pneumonia | CPT | no therapy | prospective randomized | 54 | −0.7 | −2.8 to 1.4 |
| Alexander[99] | 1996 | many | CPT | no therapy | prospective randomized | 101 | −0.6 | −1.4 to 0.2 |

CI = confidence interval.
CPT = chest physiotherapy
IPPB = intermittent positive pressure breathing

### Autogenic Drainage and Active Cycle of Breathing Technique

Like conventional CPT, autogenic drainage and active cycle of breathing technique can be performed without the use of any adjunctive equipment.[116] They can also be performed without the assistance of another person. Miller et al[117] compared autogenic drainage and active cycle of breathing technique in 18 patients (crossover design) with CF by measuring pulmonary function, patient preference, sputum weight, xenon ventilation, and clearance of radioactive aerosol. They reported that these techniques are equally effective in secretion clearance. Giles et al[118] compared conventional CPT to autogenic drainage in 10 CF patients, using a crossover design. They reported no significant difference between the treatments with regard to sputum clearance or pulmonary function. However, a transient desaturation occurred with CPT that did not occur with autogenic drainage. Savci et al[119] compared autogenic drainage and active cycle of breathing technique in prospective randomized trial over 20 days in 30 patients with chronic obstructive pulmonary disease. They reported similar improvements in pulmonary function with these 2 techniques. Cecins[120] et al compared active cycle of breathing technique using a head-down position and a horizontal position in 19 patients with bronchiectasis, and they reported no significant difference in sputum production with the 2 approaches, but a strong patient preference for the horizontal (rather than head down) approach.

### Positive Expiratory Pressure

Since the mid-1980s there has been interest in the use of PEP techniques to facilitate secretion clearance, primarily with CF patients. This topic has been reviewed in RESPIRATORY CARE.[121] Studies[90,122–141] have assessed the use of PEP therapy (Table 9), and a case series of 18 hospitalized CF patients has been reported.[142] Most commonly, a crossover study design was used, and the studies have been relatively short term. Outcome variables used to assess the effect of PEP therapy included sputum production, pulmonary function testing, clearance of a radioactive aerosol from the lungs, and the avoidance of acute exacerbations. Most of the studies compared PEP to postural drainage or conventional CPT. Although PEP therapy would allow the comparison with a sham device (and potentially even blinding), this was only done in one study. These studies report mixed results. Whereas some studies report similar outcomes for PEP and postural drainage or conventional CPT, other studies report less favorable results with PEP therapy. After reviewing these studies, I think the best that can be said is that PEP therapy may be as effective as conventional CPT. However, given the results of studies of CPT reviewed previously herein, one might question the validity of comparing PEP to CPT. It is also important to recognize that the studies of PEP have been performed primarily with patients who have a diagnosis of CF (and a few studies with chronic bronchitis or as a postoperative therapy). The role of PEP therapy in other patient populations is virtually unknown. One recurrent theme in these studies is a reported patient preference for PEP, compared to CPT, most likely because PEP is more convenient and less time consuming for the patient.

### Flutter Therapy

Interestingly, most studies of PEP therapy were reported in the mid-1980s to mid-1990s. Most studies of flutter therapy were reported in the mid-to-late-1990s (Table 10).[143–152] These studies report mixed results in a variety of patient populations. Although sham therapy would be possible to evaluate flutter therapy, most studies compared flutter to another form of secretion clearance therapy (most commonly conventional CPT). Methodologically, most of these studies are limited by crossover designs and small sample sizes. The best that can be concluded from these studies is that flutter therapy may produce similar effects on sputum production and pulmonary function as conventional secretion clearance therapies. One study[150] reported lower viscoelasticity with flutter. However, that finding did not result in improved sputum expectoration in that study. It is also of interest to note that one study[149] reported a pneumothorax in association with flutter therapy.

Table 9. Studies Evaluating the Use of PEP Therapy

| First Author | Year | Diagnosis | Control | Design | *n* | Outcome Variables | Study | Principal Findings |
|---|---|---|---|---|---|---|---|---|
| Falk[123] | 1984 | CF | CPT, FET | crossover | 14 | sputum production, transcutaneous $P_{O_2}$ | 1 tx | Mean sputum production of 10 g for CPT, 21.6 g for PEP + PD, 17.4 g for PEP, and 15 g for FET. Decrease in transcutaneous $P_{O_2}$ with CPT; increase with PEP. |
| Tonnesen[122] | 1984 | CF | CPT | before and after | 12 | sputum production, PFT | 6–9 mo | Significant reduction in residual volume with PEP. Subjective improvement in sputum production with PEP |
| Campbell[124] | 1986 | post-operative | CPT | prospective randomized | 71 | post-operative pulmonary complications | post-op course | 31% of patients in PEP + CPT developed post-operative complications, vs. 22% in the PEP group. |
| Tyrrell[125] | 1986 | CF | CPT | crossover | 16 | symptom scores, sputum production, PFT | 1 mo | No difference between PEP and CPT for any of the outcome variables. |
| Frolund[140] | 1986 | post-operative | sham | prospective randomized | 56 | atelectasis, arterial blood gases | post-op course | No difference between groups for any of the outcome variables measured. |
| Hofmeyr[126] | 1986 | CF | PD, FET | crossover | 18 | sputum production, oxygen saturation, PFT | 4 tx | Sputum production was less when PEP was used. No significant differences in oxygen saturation or PFT. |
| Oberwaldner[127] | 1986 | CF | CPT | crossover | 20 | sputum production, PFT | 18 mo | Sputum production greater with PEP. Significant increase in expiratory flows and decreased hyperinflation with PEP. |
| Van Asperen[128] | 1987 | CF | PD | crossover | 10 | sputum production, PFT | 4 wk | No significant difference in sputum production or PFT results. |
| van Hengstum[129] | 1988 | chronic bronchitis | FET | crossover | 8 | radioactive aerosol clearance | 1 tx | Significantly greater radioactive aerosol clearance with FET. |
| Kaminska[138] | 1988 | chronic bronchitis | PD | crossover | 12 | sputum production, patient's subjective assessment | 4 wk | Sputum production greater for PD than PEP in most patients. Patients found PEP convenient. |
| Christensen[137] | 1990 | chronic bronchitis | CPT | prospective randomized | 43 | pulmonary function, antibiotic and mucolytic use, acute exacerbations | 12 mo | Fewer exacerbations with PEP. Less use of antibiotics and mucolytics with PEP. Small increase in $FEV_1$ with PEP, vs small decrease with CPT. |
| Christensen[130] | 1990 | COPD | sham | prospective randomized | 47 | PFT, $P_{aO_2}$, dyspnea, sputum production, acute exacerbations | 6 mo | No difference between groups for any of the outcome variables. |
| Steen[131] | 1991 | CF | CPT, FET | crossover | 24 | sputum production, spirometry | 1 mo | No significant difference between groups for sputum production or spirometry. |
| van Hengstum[132] | 1991 | chronic bronchitis | FET/PD, no tx | crossover | 7 | radioactive aerosol clearance | 1 tx | Clearance in all 3 lung zones was largest after FET/PD, compared with PEP. PEP no different than no therapy. |
| Mortensen[133] | 1991 | CF | PD | crossover | 10 | radioactive aerosol clearance | 1 tx | Similar clearance for PEP and PD. |
| Lannefors[134] | 1992 | CF | PD, exercise | crossover | 9 | radioactive aerosol clearance, sputum production | 1 tx | No difference in radioactive aerosol clearance or sputum production between treatments. |
| Pfleger[135] | 1992 | CF | AD | crossover | 14 | sputum production, spirometry | 1 tx | Significantly more sputum produced with PEP. |
| Richter Larsen[139] | 1995 | post-operative | CPT | prospective randomized | 66 | PFT, atelectasis | post-op course | No significant difference between groups for any of the outcome variables. |
| Mellwaine[136] | 1997 | CF | CPT | prospective randomized | 40 | PFT | 1 y | Significantly improved FVC and $FEV_1$ in patients receiving PEP compared to CPT |
| Plebani[141] | 1997 | HIV | — | before and after | 8 | pulmonary infections, antibiotic courses | 12 mo | Reduction in pulmonary infections and antibiotic courses with PEP. |

PEP = positive expiratory pressure.
CF = cystic fibrosis.
CPT = chest physiotherapy.
FET = forced expiratory technique.
COPD = chronic obstructive pulmonary disease
$P_{O_2}$ = partial pressure of oxygen.
PFT = pulmonary function test
PD = postural drainage
$FEV_1$ = forced expiratory volume in the first second.
$P_{aO_2}$ = arterial partial pressure of oxygen.
tx = treatment.
AD = autogenic drainage
HIV = human immunodeficiency virus.

Table 10. Studies Evaluating Flutter Therapy

| First Author | Year | Diagnosis | Control | Design | *n* | Outcome Variables | Duration | Principal Findings |
|---|---|---|---|---|---|---|---|---|
| Chatham[143] | 1993 | post-thoracotomy | CPT | crossover | 24 | vital capacity, sputum production, breathing, chest comfort, and expectoration scores | 1 d | No additional benefit occurred with the addition of flutter to CPT. Flutter-only therapy generated the worst results. |
| Pryor[144] | 1994 | CF | ACB | crossover | 24 | sputum production, spirometry, oxygen saturation | 1 d | Greater sputum production with ACB than with flutter + ACB No spirometry or oxygen saturation differences between treatments. |
| Girard[145] | 1994 | asthma | — | before and after | 20 | spirometry | 30–45 d | Significant spirometry improvement with flutter therapy. |
| Swift[146] | 1994 | asthma | sham | crossover | 20 | peak flow, salbutamol use, questionnaires | 7 d | No difference in peak flow or salbutamol use between flutter and sham therapy. |
| Konstan[147] | 1994 | CF | cough, PD | crossover | 18 | sputum production | 1 tx | Significantly more sputum expectorated with flutter than with cough or PD. |
| Homnick[148] | 1998 | CF | CPT | prospective randomized | 22 | spirometry, length of hospitalization, number of respiratory treatments, clinical score | Length of hospital stay | No significant differences between flutter and CPT for any outcome variables. |
| Burioka[149] | 1998 | pan-bronchiolitis | cough | crossover | 8 | pulmonary function, sputum production, blood gas values, symptom scores | 7 d | Sputum production and peak flow improved with flutter. One patient developed pneumothorax during flutter therapy. |
| App[150] | 1998 | CF | AD | crossover | 14 | pulmonary function, sputum production, sputum viscoelasticity | 7 d | No significant differences in pulmonary function or sputum volume. Sputum viscoelasticity lower with flutter. |
| Gondor[151] | 1999 | CF | CPT | prospective randomized | 23 | spirometry, oxygen saturation, 6-min walk | 14 d | Similar improvements in spirometry and 6-min walk with flutter and CPT. |
| Bellone[152] | 2000 | chronic bronchitis | PD | crossover | 10 | pulmonary function, sputum production, oxygen saturation | 1 tx | No significant differences in pulmonary function or oxygen saturation. Small but significantly greater sputum production with flutter. |

CF = cystic fibrosis.
AD = autogenic drainage.
PD = postural drainage.
CPT = chest physiotherapy.
ACB = active cycle of breathing.
tx = treatment.

### High Frequency Chest Compression

Since the early 1990s there has been clinical interest in techniques that produce high-frequency chest compression (HFCC), also called high-frequency chest wall oscillation.[153–155] In a before-and-after therapy design, Warwick and Hansen[156] reported the experience of 15 CF patients who used HFCC for 22 months and reported improvements in pulmonary function with this therapy. Arens et al[157] randomized 50 CF patients admitted to the hospital for acute pulmonary exacerbation to receive either HFCC or CPT. They reported similar improvements in clinical status and pulmonary function for the patients receiving HFCC and CPT, and speculated that HFCC might be an adequate alternative to hospitalized CF patients. Braggion et al[158] compared postural drainage, PEP, and HFCC, us-

ing a crossover design, with 16 CF patients, and reported no significant differences in sputum production between the 3 techniques. Kluft et al[159] compared HFCC and CPT using a crossover design in 29 CF patients, and reported significantly more sputum production with HFCC. A concern with HFCC is the potential for reduced end-expiratory lung volume and resultant airway closure. Jones et al[160] reported a 30% reduction in end-expiratory lung volume with the application of HFCC. However, Perry et al[161] reported that this effect on end-expiratory lung volume is prevented by application of a modest amount of positive end-expiratory pressure. Whitman et al[162] studied sputum clearance using HFCC in 9 mechanically ventilated patients and reported that this technique is equally efficacious to CPT.

### Intrapulmonary Percussive Ventilation

Intrapulmonary percussive ventilation has been evaluated in a case series[163] and several studies. Van Hengstum[164] reported no effect of oral high-frequency oscillation combined with forced expiration maneuvers on tracheobronchial clearance in chronic bronchitis. Natale et al[165] compared intrapulmonary percussive ventilation to CPT in a crossover design with 9 CF patients and reported that intrapulmonary percussive ventilation was as effective as CPT on spirometry and sputum expectoration. Homnick et al[166] randomized CF patients to receive intrapulmonary percussive ventilation or CPT for 6 months. No significant differences were reported for spirometry, number of hospitalizations, use of oral or intravenous antibiotics, or anthropometrics. Scherer et al,[167] using a crossover design study, compared high-frequency oral airway oscillation, high-frequency chest wall oscillation, and standard CPT in 14 pediatric CF patients. They reported that the 3 treatment modalities had similar effects on sputum production.

### Manual Hyperinflation

Denehy[22] conducted a narrative review of manual hyperinflation and concluded that considerable controversy exists regarding the safety and effectiveness of this therapy for intubated patients. Jones et al[168] reported an improvement in lung mechanics and arterial oxygen with this technique. However, Novak et al[169] reported that manual hyperinflation had no sustained effect on gas exchange or pulmonary mechanics. Moreover, Singer et al[170] reported that lung hyperinflation is usually not achieved with this technique and that significant changes in cardiac output occur when hyperinflation is achieved. Furthermore, Clarke et al[171] raised concern regarding the safety of this technique, because of the high tidal volume and peak inflation pressures that are used. Others have also reported deterioration in gas exchange associated with this technique.[34]

### Mechanical In-Exsufflation

Manually assisted cough and the mechanical in-exsufflator are techniques to assist secretion clearance in patients with neuromuscular disease.[172] The mechanical in-exsufflator has been popularized by Bach as a secretion clearance methodology.[172–177] Although use of the mechanical in-exsufflator has become an accepted part of the respiratory armamentarium for patients with neuromuscular disease, the evidence is anecdotal, with only nonrandomized case series having been reported.

### Observations and Limitations of this Review

There are a number of methodological limitations of the literature reporting studies of the use of secretion clearance techniques. Most of the studies are small: many include fewer than 20 subjects. Most use crossover designs rather than prospective randomized controlled designs. In most cases, sham therapy was not used, although this is possible for techniques such as PEP and flutter. In many cases, one technique was compared to another (for example, CPT vs PEP). Few compared a therapy to no therapy. Many studies were limited to short-term outcomes such as sputum clearance with a single treatment session. It might be argued that short-term outcomes such as sputum clearance or radioactive aerosol clearance are irrelevant and that the focus should be on long-term outcomes such as disease progression, quality of life, and patient satisfaction. The focus of secretion clearance techniques has been the amount of sputum produced. Although it seems obvious, increased secretion clearance in diseases such as CF has not been shown to affect disease progression. In many sputum-producing diseases, the presence of secretions in the airway may be a symptom of disease rather than a cause of disease.

It is recognized that conducting a methodologically strong study (ie, placebo-controlled prospective randomized controlled trial) with an adequate sample size and important outcomes (eg, disease progression, morbidly, or mortality) would prove difficult. The study would be expensive and industrial support such as occurs with drug studies is not likely. Moreover, secretion clearance is an integral component of disease management of patients with sputum hypersecretion, raising serious ethical concerns in the minds of clinicians and patients.

Several limitations of this review are acknowledged. First, it was conducted by a single author and different conclusions might be reached by others reviewing this literature. The issue of reviewer bias is real. As a respiratory therapist with more that 25 years of experience, I embarked on this review with a bias favoring secretion clearance techniques. Every attempt was made to provide a comprehensive and balanced review, but it is possible

that some important studies were missed. No attempt was made to include abstracts from scientific meetings or to include data from unpublished trials. Few limitations were placed on the quality of studies included in this review—the attempt was to be comprehensive rather than selective. It is noted that systematic reviews that set rigid criteria for selection of studies excluded all published studies because of poor methodological scores.[30] Finally, although some quantitative results are provided, this review is not a meta-analysis.

### Lack of Evidence Versus Lack of Benefit

Based on this review, I conclude that there is insufficient evidence to support the use of any secretion clearance technique. Most of the studies are observational trials (crossover studies) and physiologic studies (sputum clearance, radioactive aerosol clearance, or spirometry) with small sample sizes. Moreover, there are not consistent findings, with some studies reporting benefit and others reporting no benefit. At best, the literature on this topic is disappointing.

This raises a very important question for the clinician. Does the lack of evidence mean lack of benefit? Is the lack of evidence due to study methodology, or is there really no benefit from these techniques? Given the lack of evidence, as a clinician I suggest the following hierarchy of questions that might be asked when considering secretion clearance therapy for a patient.

1. Is there a pathophysiologic rational for use of the therapy? Is the patient experiencing difficulty clearing secretions? Are retained secretions affecting lung function in an important way such as gas exchange or lung mechanics? Note that the production of large amounts of sputum does not necessarily mean that the patient is experiencing difficulty clearing sputum.

2. What is the potential for adverse effects of the therapy? Which therapy is likely to provide the greatest benefit with the least harm?

3. What is the cost of the equipment for this therapy? Some of these devices are quite expensive (Table 11). The cost of the device may not be covered by third-party insurers, resulting in considerable out-of-pocket expense for the patient or the hospital.

4. What are the preferences of the patient? Lacking evidence that any technique is superior to another, patient preferences are an important consideration. Validation of an instrument for measuring patient satisfaction with secretion clearance techniques has been published.[48]

When a clinical decision is made to try a secretion clearance technique, a simple clinical trial can be conducted (an *n* of 1 trial).[178–182] For example, imagine that a decision is made to try flutter therapy for a patient. The clinician and patient agree that a clinically useful outcome measure is sputum production. A 12-week trial is designed. For one week, the only sputum clearance technique used will be huff coughing. For a second week, flutter therapy will be used as provided by the manufacturer. For a third week, the flutter device will be used with the oscillating ball removed (sham therapy). The patient, who is naive to the therapy, does not know whether the device should be used with or without the oscillating ball. The order of treatments is randomized (the patient flips a coin) and the sequence is repeated 4 times. Each day, the sputum produced during the therapy session is weighed. A diary is also kept in which events such as chest infections are logged. At the end of 12 weeks, the results are analyzed (which may include statistical analysis), reviewed together by the clinician and patient, and a collaborative decision is made regarding the benefit of the therapy. In this manner, an objective decision is made regarding the benefits of the therapy for this individual patient. Such an approach may be particularly useful for techniques such as postural drainage, in which variability of patient response has been reported.[183,184]

Table 11. Cost of Some Secretion Clearance Devices

| Device, Manufacturer, Location | Price ($) |
|---|---|
| Flutter, Axcan Scandipharm (Birmingham, Alabama) | 38.75 |
| TheraPEP, DHD Healthcare (Wampsville, New York) | 24.75 |
| Vest Airway Clearance System, Advanced Respiratory (St. Paul, Minnesota) | 15,900 |
| Intrapulmonary Percussive Ventilator, Percussionaire Corporation (Sandpoint, Idaho) | 3,500 |
| In-Exsufflator, Emerson Corporation (Cambridge, Massachusetts) | 4,350 |

### Summary

Despite the clinical observation that retained secretions are detrimental to respiratory function and despite anecdotal associations between secretion clearance and improvements in respiratory function, there is a dearth of high-level evidence to support any secretion clearance technique. This is problematic, given that a substantial portion of respiratory care practice is related to secretion clearance. Although lack of evidence does not mean lack of benefit, it is desirable to have better evidence to support this practice. Appropriately powered and methodologically sound research is desperately needed on this subject.

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### Discussion

**Durbin:** As usual, Dean, you've done an admirable job of detailing an immense amount of literature, raising the sound and the fury and signifying nothing. I challenge one of the assumptions that are made in these analyses, which you pointed out. The assumption is that if the confidence interval overlies zero—indicating no treatment effect—that you need to be very concerned that the effect observed in the study is not real. I think that's a harsh standard for such small studies. Another interpretation might be that the number of patients tested is simply too small to identify either differences between individual patients or the group as a whole.

**Hess:** That's absolutely correct. And the reason why the 95% confidence intervals are so wide in these studies is, first of all, that there is a lot of variability in many of these studies. The standard deviations they report are sometimes nearly as large as the means. And then, secondly, they are very small sample sizes. Certainly those confidence intervals would shrink if they studied 200 patients rather than studying 10 patients—you would hope. But we don't know.

**Tonelli:** I think this is actually a very interesting and challenging area for evidence-based medicine, and let's just focus on, say, the CF patients and airway clearance. First, I think the study most of us would design to try to answer that question would be a long-term, large, randomized controlled trial of particular techniques, compared to placebo or sham. That study won't get done for a variety of reasons. One, I would suggest, is that probably there's not clinical equipoise among CF physicians, for they largely believe that some form of airway clearance is effective. But you also put your finger on a large problem in terms of trying to study these in any other fashion, and that is that there's a tremendous amount of individual variability in terms of a patient's perceived benefit, and even from objective measures in terms of improvement of $FEV_1$, between the various techniques, such that there are patients who swear by one and will not, under any circumstance, use another. I actually think this may be one area where the standard tools of evidence-based medicine are likely to fail us, and perhaps the *n* of 1 study is actually the appropriate one here, and that, in fact, you need to find a therapy that seems to work for a particular individual patient, primarily because the perception of whether it works will depend on whether they actually use it.

**Hess:** I think that because of the small sample sizes and the large standard deviations and so forth, we can't say that any of these therapies are not effective, and I guess I probably want to go on record that I'm not saying that any of these therapies are not effective. What I'm saying is that we

have insufficient evidence to say that many of them are effective. And I agree that it would be very difficult to do the type of studies that many of us would like to see done. They would be very expensive and we would perhaps have a very difficult time enrolling patients, because many of the clinicians caring for those patients, and the patients themselves, would view the intervention as unethical.

**Tonelli:** Yes, and I think what we're left with in these types of situations is to say, "OK, we don't have proof of benefit." One might argue that we also don't have proof of harm, and I would say there are different approaches as to what to do when you're in that situation. One is to throw up your hands and say, "I'm not going to do anything," and the other is to try to tailor the therapy based on clinical experience, observations, and interaction with the patients. I think for this particular therapy, if we wait around until there's proof of efficacy—that will never come for these therapies, and in particular for CF.

**Hess:** Another thing we need to consider is the cost of some of these new therapies. Some of the new devices are very expensive, and pressure is being bought to bear on third-party payers, for example, to cover some of them, some of which cost in excess of $10,000. There are only a few—less than five—studies of any type in the literature that have looked at these. Of those 5, perhaps "studies" isn't even the best word; "reports" may be a better word. Many of them are nothing more than case reports and anecdotal evidence.

**Ellrodt:** For these devices, do they need to go through some sort of Food and Drug Administration (FDA) review?

**Hess:** They do. In fact, they are all FDA-approved.

**Ellrodt:** Despite the lack of evidence? Does the FDA have evidence as to their success? The FDA is pretty good, certainly, with drugs. They may not be as good with devices in terms of efficacy. What's the story?

**Hess:** I think that's the answer. I think that, essentially, for these devices all the manufacturer has to do is to convince the FDA that the device works the way that it is labeled to work. And I don't think there's much more beyond that that needs to be done. They do not need to submit to the FDA the level of evidence required for a new drug.

**Chatburn:** An issue that we seem to keep dancing around is the cost. It's not just the cost of the device itself; it's the cost of the labor associated with supplying it. And people who are in administrative positions are caught in this double bind, where they are forced to cut labor costs and stop doing things that don't have any proven effectiveness, and yet we keep running up against a wall of how you change behaviors on the part of clinicians when you don't have any good evidence to do that. So it's sort of a conundrum. Do you have any advice as to how you could approach that? Was there anything in the literature that talked about cost as a deciding factor?

**Hess:** By and large in these studies, cost was ignored. The Alexander study[1] looked at randomizing patients to CPT or no CPT: a physician wrote the order for CPT, then a pulmonary fellow randomized the patient either to get the CPT or not. And then they looked at things like the incidence of atelectasis, the hospital length-of-stay, and so forth, and found there was no difference between those who got CPT and those who did not. They then calculated what I would say were some very inflated cost savings. You know; they went through this thing of, "We pay our respiratory therapists this much, and we stopped this many treatments a year." They did this math and concluded, "There are this many patients in the United States, so we'll save millions of dollars by eliminating this."

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**Chatburn:** Only if you get rid of the full-time equivalents (employees) associated with it—only they never do that.

**Ellrodt:** They actually did that.

**Guyatt:** Two points. One: when you talk about the expense of conducting the studies, if indeed you could cut back on employees, you have to put that beside the yearly expense of administering these therapies that are done to individuals; most of the time the cost of doing the studies is minuscule relative to years and years of administering the therapies. The second point is that in areas where clinicians have been convinced of the effectiveness, or it's their bailiwick, and so very difficult to mount trials, one strategy is to begin with a trial that takes the conventional or maximal intervention, and gives less of that intervention, or the minimum that people will find acceptable. That can be a first step if people find it unacceptable to not administer the intervention at all.

**Hess:** Good points. Thank you.

# Chronic Obstructive Pulmonary Disease Management: The Evidence Base

Neil R MacIntyre MD FAARC

**Introduction**
**Establishing the Evidence Base**
**Management of Chronic Disease**
**Bronchodilator Therapy**
**Corticosteriods**
**Mucolytics**
**Oxygen**
**Rehabilitation**
**Non-Invasive Positive Pressure Ventilation at Night**
**Management of Acute Exacerbations of COPD**
**Bronchodilators**
**Corticosteriods**
**Antibiotics**
**Non-Invasive Positive Pressure Ventilation**
**Summary**

**In long-term management of stable chronic obstructive pulmonary disease (COPD), a number of medications improve pulmonary function test results. The long-term clinical benefits of those drugs would seem intuitive, but there is very little strong evidence that long-term outcomes in COPD are substantially affected by those drugs. Nevertheless, symptom improvement such as dyspnea reduction is certainly strong reason to use those agents. The 2 most compelling bodies of evidence in stable COPD are for oxygen therapy in the chronically hypoxemic patient and pulmonary rehabilitation to improve exercise tolerance and dyspnea. Inhaled corticosteroids also appear to be useful in patients at risk for frequent exacerbations. In acute exacerbations, the rationale for therapy comes in part from the large body of literature regarding acute asthma therapy. Bronchodilator therapy and corticosteroids both seem to reduce the severity and the duration of exacerbations. Moreover, routine antibiotic use seems beneficial, and the role of noninvasive positive-pressure ventilation with patients suffering impending respiratory failure from acute COPD exacerbations is well supported by the literature.** *Key words: chronic obstructive pulmonary disease management, evidence-based medicine, COPD.* [Respir Care 2001;46(11):1294–1303]

## Introduction

Chronic obstructive pulmonary disease (COPD) is a spectrum of disorders that results in air flow obstruction.[1] At one end of the spectrum is chronic bronchitis, which is characterized by airway inflammation, mucus hypersecretion, and airway reactivity. At the other end of the spectrum is emphysema, characterized by alveolar destruction and small airway abnormalities. Air trapping and hyper-

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A version of this paper was presented by Dr MacIntyre during the RESPIRATORY CARE Journal Conference, Evidence-Based Medicine in Respiratory Care, held April 20-22, 2001, Banff, Alberta, Canada.

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inflation are common at both ends of the spectrum. In reality, most COPD patients have features of both.

The American Thoracic Society defines chronic bronchitis clinically as being a productive cough for ≥ 3 mo/yr for > 2 years.[1] Physiologically, COPD is characterized by an $FEV_1$ (forced expiratory volume in the first second) < 70–72% of the forced vital capacity. In addition, enlarged residual volumes are common and a reduced diffusing capacity is present when there is substantial emphysema. Radiologically, COPD is manifest by hyperinflation and bronchial wall thickening.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project of the National Heart, Lung, and Blood Institute and the World Health Organization, has established a series of global obstructive lung disease guidelines for the management of COPD.[2] These guidelines classify COPD into 4 stages, based on symptoms and spirometry (Table 1).

COPD is punctuated by periodic acute exacerbations (AECOPD).[3] These are usually triggered by infections, but pneumothoraces, heart failure, pulmonary emboli, and other noninfectious processes can present similar findings. Acute exacerbations are often characterized by the Winnipeg Criteria.[3,4] Using those criteria, a Type I acute exacerbation has any one of: increased dyspnea, increased sputum volume, or increased sputum purulence. A Type II exacerbation would be two of those symptoms. A Type III exacerbation has at least one of those symptoms in conjunction with a fever or symptoms of an upper respiratory infection.

Table 1. COPD Severity Classification According to the GOLD Guidelines[2]

| Stage | Characteristics |
|---|---|
| 0: At Risk | Normal spirometry<br>Chronic symptoms (cough, sputum production) |
| I: Mild COPD | $FEV_1/FVC < 70\%$<br>$FEV_1 \geq 80\%$ of predicted<br>With or without chronic symptoms (cough, sputum production) |
| II: Moderate COPD | $FEV_1/FVC < 70\%$<br>$30\% \leq FEV_1 < 80\%$ of predicted<br>(IIA: $50\% \leq FEV_1 < 80\%$ of predicted)<br>(IIB: $30\% \leq FEV_1 < 50\%$ of predicted)<br>With or without chronic symptoms (cough, sputum production, dyspnea) |
| III: Severe COPD | $FEV_1/FVC < 70\%$<br>$FEV_1 < 30\%$ of predicted, or the presence of respiratory failure,* or clinical signs of right heart failure |

GOLD = Global Initiative for Chronic Obstructive Lung Disease.
COPD = chronic obstructive pulmonary disease
$FEV_1$ = forced expiratory volume in the first second.
FVC = forced vital capacity
*Respiratory failure = arterial partial pressure of oxygen < 60 mm Hg, with or without arterial partial pressure of carbon dioxide > 50 mm Hg while breathing air at sea level

COPD affects as much as 10% of the United States population and accounts for substantial costs, morbidity, and mortality.[1] Indeed, COPD ranks as the fourth leading cause of death among Americans, and annual medical expenditures are estimated as high as 20 billion dollars. For these reasons, it is critical for the health care system to provide treatments and disease management for those patients.

## Establishing the Evidence Base

The present review is based on an evidence review from several sources (Table 2). There are limitations to this process. First, although extensive, it is not necessarily a comprehensive systematic evidence-based review. Formal comprehensive reviews require specialized centers of expertise, large staff, and the capability of doing sophisticated meta-analyses. A second limitation is that not all management topics are covered. The role of surgery, for instance, is not addressed. A third limitation is that the evidence presented here comes exclusively from clinical studies, usually randomized control trials. A large body of animal data, bench data, and observational experience is thus not included. Those "lower levels" of evidence, however, must be considered in filling in the knowledge gaps to develop effective practice guidelines. Finally, it must always be remembered that absence of proof is not proof of absence. Specifically, because evidence supporting a particular practice may be absent or poor does not necessarily mean that the practice is bad or useless. It may mean merely that the practice has not been adequately studied.

## Management of Chronic Disease

### Bronchodilator Therapy

The commonly used bronchodilators are $\beta$ agonists (usually inhaled, occasionally oral or intravenous), anticholin-

Table 2. Sources of Evidence

| |
|---|
| American Thoracic Society COPD recommendations[1] |
| ACCP/AACVPR evidence-based guidelines for pulmonary rehabilitation[5] |
| AHCPR evidence-based report on acute exacerbations of COPD[3] |
| Cochrane Libraries collection of evidence-based reviews on COPD through 2000 (http://www.cochranelibrary.com/abs/titlelist.htm) |
| Clinical evidence 2000 (BMJ Publishing Group) (http://www.clinicalevidence.org) |
| MEDLINE search for COPD evidence-based reviews since 1991 |

ACCP/AACVPR = American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation
AHCPR = Agency for Health Care Policy and Research

ergies (inhaled), and theophylline (oral). All of these agents have been used in clinical practice for a number of years and have been evaluated in a wide variety of ways. Indeed, much of the rationale supporting the use of these drugs in COPD has been an extrapolation of the clinical data derived from studies of asthma patients.[6] The argument goes that COPD patients have chronically inflamed airways (and often evidence of hyperreactivity and/or bronchodilator responsiveness), so bronchodilators effective in asthma are often assumed to be effective in COPD.

Clinical studies of these drugs in COPD are usually of 3 types: drug versus placebo; drug 1 versus drug 2; and drug 1 plus drug 2 versus drug 1 or drug 2 alone. It should be noted that, in most of these studies, only short-term effects of the drug (either hours or over a few weeks) have been evaluated. Moreover, physiologic measurements (eg, $FEV_1$) are the usual end points, although more recent studies have begun to include functional measurements such as exercise tolerance, quality of life, or symptoms assessments. Very few studies have looked at the long-term progression of disease and whether improvements in short-term intermediate end points translate into meaningful long-term outcome improvements.

Another important point to remember is that a statistically significant change in an end point may not necessarily mean that a clinically important benefit has occurred. For example, a large trial may show that $FEV_1$ has significantly improved by a few milliliters, but this change would probably have little or no impact on functional capabilities or ultimate outcome. When interpreting the results of clinical trials, we must keep that concept in mind.

$\beta$ agonists have been compared to placebo in COPD in a number of studies, dating back many years.[7–12] There is a consistent finding that short-acting agents improve pulmonary function test (PFT) values in the immediate testing period (before- versus after-administration of the drug). Longer-term studies have suggested that the improvement in $FEV_1$ with a $\beta$ agonist is better maintained if the drug is given on an as-needed basis, as opposed to routinely.[13,14] This probably reflects the phenomenon of tachyphylaxis known to occur with prolonged adrenergic stimulation.

More recent studies have shown that long-term use of the long-acting $\beta$ agonist salmeterol improves PFT values and maintains that improvement over a number of weeks.[15–19] Salmeterol also appears to decrease the use of rescue albuterol—an indication that not only is air flow obstruction improved but that the patient's symptomatic needs for additional bronchodilator therapy seem reduced.[19,20]

Anticholinergics have also been compared to placebo in a number of studies. Like albuterol, ipratropium has been shown to improve PFT values in an immediate before-and-after fashion.[7,8,21] Other studies have also shown that PFT values and symptoms can be improved and maintained over a number of weeks with routinely administered anticholinergics.[15,19,22] In the National Institutes of Health-sponsored Lung Health Study, which followed a large number of COPD patients for over 5 years, the use of ipratropium was associated with a small but persistent $FEV_1$ improvement during the follow-up period.[23]

Theophylline has been compared to placebo and, like the other bronchodilators, has been shown to improve PFT values during the immediate testing period.[24–26] One study also found that diaphragmatic strength was improved after treatment with theophylline.[26] Finally, one other study showed that, although theophylline over a several-week period did not improve PFT values, dyspnea seemed improved.[27] $\beta$ agonists have been compared to ipratropium in a variety of studies. Most of these studies suggest that the pulmonary function changes seen during the follow-up period were similar, regardless of which drug was used.[8,28,29] One study suggests that albuterol decreased airway reactivity more than ipratropium.[7] Another study suggests that ipratropium lasts longer.[21] Rennard et al analyzed 7 trials of albuterol versus ipratropium and concluded that there were statistically significant improvements in PFT values with both drugs but that the ipratropium treatment seemed to be associated with a statistically significant (but questionably clinically important) improvement beyond that seen with albuterol.[30] More recently, salmeterol was shown to have a much longer duration than ipratropium.[15]

Other 2-drug comparisons have shown that albuterol seems equal to theophylline for PFT effects over the short term,[31] that long-acting $\beta$ agonists (salmeterol or formoterol) appear to be better than ipratropium for pulmonary function changes and symptoms over a longer period of time,[19,32] and that a new long-acting anticholinergic, tiotropium, resulted in better $FEV_1$ and less rescue albuterol than ipratropium.[33]

In comparing combinations versus single drug therapy, a number of studies showed that albuterol plus ipratropium together gave better pulmonary function results than either drug alone.[28,29,34] One study, however, suggested that if the individual drug was pushed to higher doses, the addition of the second drug did not offer much benefit.[8] Albuterol and theophylline also appear better than each alone.[31] Karpel et al in 1994 compared 4 combinations of therapy: albuterol plus ipratropium plus theophylline; theophylline plus albuterol; ipratropium alone; and placebo.[35] In general: 3 drugs produced better $FEV_1$ than did 2 drugs; 2 drugs produced better $FEV_1$ than did 1 drug; and 1 drug produced better $FEV_1$ than did placebo. Ipratropium alone had a lower heart rate effect than the combination of albuterol and theophylline.

In summary, ample evidence supports the use of the various bronchodilators in COPD. All 3 classes ($\beta$ ago-

nists, anticholinergics, and theophylline) are effective, and combinations of currently approved dosing regimens may be superior to single agents. However, it is not clear if these combinations would be superior to pushing the dose of any one agent to high levels. In mild COPD, as-needed use of a $\beta$ agonist has better long-term effects than routine regular use. However, if a COPD patient finds that regular bronchodilators are needed, evidence is strong that long-acting $\beta$ agonists and/or anticholinergics are more effective in optimizing $FEV_1$ and symptoms than are regular short-acting agents. Theophyllines are associated with more side effects than other agents.

### Corticosteriods

The rationale for corticosteroids in COPD is similar to that for their use in asthma. Specifically, chronically inflamed COPD airways may be responsive to anti-inflammatory agents such as oral or inhaled corticosteroids. Supporting this concept is the observation that a majority of COPD patients have an airway constriction response to methacholine.[23]

Callahan et al in 1991 performed a meta-analysis of 15 studies performed between 1966 and 1989, comparing oral corticosteroids to placebo in COPD patients.[36] He defined response as a 20% increase in $FEV_1$ and defined an effect size as the percent responding to corticosteroids minus the percent responding to placebo. This analysis indicated a range of effect sizes favoring corticosteroids, from 0% to 56%, with a weighted mean effect of 11% (95% confidence interval [CI] 4–18%). Put another way, their analysis suggests that the use of corticosteroids improves pulmonary function in approximately 11% of COPD patients. Unfortunately, there is no way to identify a priori who those 11% are. Empirical clinical practice (supported by the recent GOLD recommendations[2]) often consists of trying corticosteroids in patients who either do not seem optimally controlled on bronchodilators or who experience frequent (> 2/y) exacerbations that respond to corticosteroids. That this approach may not be optimal is supported by the results of a recent study in 38 "corticosteroid-dependent" COPD patients, which found no change in $FEV_1$, dyspnea, or quality of life when the corticosteroids were withdrawn.[37]

Inhaled corticosteroids have been extensively studied in stable COPD.[38–44] A meta-analysis of 3 small studies conducted between 1983 and 1996 suggested a small benefit to inhaled corticosteroids in reducing the rate of $FEV_1$ decline.[44] More recent and larger long-term studies are summarized in Table 3. In general, those studies suggest that inhaled corticosteroids, though not significantly affecting the rate of $FEV_1$ decline over time, do offer benefit in patients with stable COPD by reducing the incidence of exacerbations.

Three studies have looked at the effects of oral versus inhaled corticosteroids in COPD patients. In one small study there was no difference observed.[45] In the other two, however, it appeared that the oral form of the drug improved $FEV_1$ more than the inhaled form.[46,47]

### Mucolytics

Poole and Black reviewed the Cochrane Airway Group register to May 1999.[48] This was a systematic review of 15 randomized controlled trials that showed statistically significant (although clinically small) benefits from mucolytics. Specifically, there were reduced exacerbations (95% CI 0.1–0.11), fewer days of disability (95% CI 0.61–0.69), and improved $FEV_1$ (95% CI 0.039–0.075) associated with the use of mucolytics. There did not appear to be any measurable differences among the mucolytics used.

### Oxygen

In fixed hypoxemia (resting partial pressure of oxygen [$P_{O_2}$] < 55 mm Hg) there are 2 very compelling large-scale randomized clinical trials indicating that long-term use of continuous oxygen therapy improves outcome.[49,50] There are fewer data evaluating the use of long-term oxygen therapy in patients with borderline hypoxemia ($P_{O_2}$ 55–65 mm Hg). In one study of 135 patients with those $P_{O_2}$ levels, a randomized controlled trial of oxygen versus placebo showed no effect on outcome.[51]

Two special situations with hypoxemia deserve additional comment: nocturnal oxygen desaturation and exercise oxygen desaturation. Adequate daytime oxygenation but nocturnal oxygen desaturation has been observed in a sizeable proportion of COPD patients. Only one study, however, involving 38 patients, looked at the long-term effects of supplying oxygen in such patients.[52] In that study, 3 L/min nocturnal oxygen (versus no therapy) resulted in a lower pulmonary artery pressure in the treated group but no change in outcome. In a review of the literature, O'Donohue and Bowman, in 1999, recommended that oxygen be used with nocturnal oxygen desaturation only if important signs or symptoms of hypoxemia (erythrocytosis, pulmonary artery pressure hypertension) were present.[53]

A number of COPD patients with adequate resting $P_{O_2}$ desaturate their hemoglobin with exercise. There are a number of studies showing that supplemental oxygen during these exercise desaturations improves oxygenation and the ability to perform exercise.[54] However, only one blinded crossover study has been done on long-term oxygen therapy in such patients.[55] In that study, oxygen or placebo was randomly supplied to patients with exercise desaturation, to be used during the day as much as possible. In a several-week follow-up period there was no significant change in symptoms or walk distance between the 2 treat-

Table 3. Inhaled Steroids in COPD: Effects on $FEV_1$ and Acute Exacerbations of COPD

| Study | Treatment (μg/d) | *n* | $FEV_1$ (% of predicted) | $FEV_1$ change (steroids vs placebo) | Exacerbations (steroids vs placebo) |
|---|---|---|---|---|---|
| Burge et al[40] | FP 1,000 | 751 | 50 | +9 mL/y | reduced 25%* |
| Paggiaro et al[38] | FP 1,000 | 281 | 35–90 | +190 mL/y | reduced 26%* |
| Vestbo et al[41] | BUD 800 | 290 | 86 | −3 mL/y | reduced 4% |
| Pauwels et al[42] | BUD 800 | 912 | 77 | +12 mL/y | NR† |
| Lung Health[43] | TAA 1,200 | 1,116 | 30–90 | +3 mL/y | reduced 40%* |

$FEV_1$ = forced expiratory volume in the first second
FP = fluticasone propionate
BUD = budesonide
TAA = triamcinolone acetate
*$p < 0.05$.
†not reported

ments. It should be noted, however, that the patients were not put through a formal exercise rehabilitation program and, indeed, there are no randomized trials of oxygen therapy under those circumstances.

In summary, the evidence is strong that continuous oxygen therapy improves outcome in patients with resting hypoxemia below $P_{O_2}$ 55 mm Hg. Evidence is less clear supporting the use of supplemental oxygen in COPD patients with exercise or nocturnal desaturation. However, physiologic data clearly support the use of supplemental oxygen under those circumstances if there is evidence of right ventricular dysfunction, pulmonary hypertension, or polycythemia. Moreover, short-term data support the use of oxygen in exercise desaturation patients undergoing exercise training.

### Rehabilitation

In 1997, the American College of Chest Physicians and the American Association for Cardiovascular and Pulmonary Rehabilitation published an extensive evidence-based medicine review of pulmonary rehabilitation.[5] Table 4 summarizes their findings. They concluded that very strong evidence exists supporting the use of pulmonary rehabilitation to improve exercise tolerance and reduce dyspnea in COPD patients. There was also good evidence indicating that pulmonary rehabilitation reduced exacerbations and improved the quality of life of COPD patients. Although psychologic function was clearly found to be improved after pulmonary rehabilitation, the review suggested that the improvement was a result of education and exercise conditioning and that there was not strong evidence to support formal psychosocial programs for COPD patients. Moreover, the review did not find evidence that pulmonary rehabilitation reduced mortality. In an extensive meta-analysis of the role of exercise conditioning in COPD patients, Lacasse et al also found strong support for the use of exercise training in COPD patients.[56]

In summary, the evidence is strong that pulmonary rehabilitation improves exercise tolerance, psychosocial function, and dyspnea and that pulmonary rehabilitation reduces the need for acute hospitalizations.

### Noninvasive Positive Pressure Ventilation at Night

The concept behind nocturnal noninvasive positive pressure ventilation (NPPV) in stable COPD patients is that "resting" the muscles at night might improve daytime symptoms. One small study indicated over a 6-week period that in hypercarbic COPD patients nocturnal NPPV did improve daytime arterial partial pressure of carbon dioxide values.[57] In contrast, several other studies of the same patient population using nocturnal NPPV did not find an effect.[58–60] The evidence is thus incomplete and contradictory regarding this modality in otherwise stable COPD patients.

## Management of Acute Exacerbations of COPD

### Bronchodilators

Much of the rationale for acute bronchodilator use in AECOPD comes from the asthma literature. The concept is that the smooth muscle reactivity, airway inflammation, and mucus production characteristic of AECOPD is, in many ways, similar to asthma and thus should respond to bronchodilator therapy.

As with stable COPD, the studies of AECOPD are generally of 3 types: drug versus placebo; drug 1 versus drug 2; and drug 1 plus drug 2 versus drug 1 or drug 2 alone. It must be pointed out, however, that these studies have been almost exclusively done in emergency rooms or in-patient facilities and are almost always done in the context of other treatments. Thus, there is rarely a true "placebo" present in that "standard" bronchodilator therapy; corticosteroids and other measures are usually being given at the

Table 4 Summary of Recommendations and Evidence Grades* from the ACCP/AACVPR Pulmonary Rehabilitation Guidelines for COPD Patients[5]

| Component/Outcome | Recommendations | Grade |
|---|---|---|
| Lower extremity training | Lower extremity training improves exercise tolerance and is recommended as part of pulmonary rehabilitation. | A |
| Upper extremity training | Strength and endurance training improves arm function. Arm exercises should be included in pulmonary rehabilitation. | B |
| Ventilatory muscle training | Scientific evidence does not support the routine use of ventilatory muscle training in pulmonary rehabilitation; it may be considered in selected patients with decreased respiratory muscle strength and breathlessness | B |
| Psychosocial, behavioral, and educational components and outcomes | Evidence does not support the benefits of short-term psychosocial interventions as single therapeutic modalities. Longer-term interventions may be beneficial. Expert opinion supports inclusion of education and psychosocial intervention components in pulmonary rehabilitation. | C |
| Dyspnea | Pulmonary rehabilitation improves the symptom of dyspnea | A |
| Quality of life | Pulmonary rehabilitation improves health-related quality of life | B |
| Health care utilization | Pulmonary rehabilitation has reduced the number of hospitalizations and days of hospitalization | B |
| Survival | Pulmonary rehabilitation may improve overall survival | C |

*Evidence Grades
A: Scientific evidence provided by well designed, well conducted, controlled trials (randomized and nonrandomized) with statistically significant results that consistently support the guideline recommendation
B: Scientific evidence provided by observational studies or by controlled trials with less consistent results to support the guideline recommendation
C: Expert opinion that supports the guideline recommendation because the available scientific evidence did not present consistent results or because controlled trials were lacking.

same time. Some of the negative results reviewed below should be evaluated in that context.

The anticholinergic glycopyrrolate[61] and ipratropium[62,63] have both been found to improve $FEV_1$ faster than placebo during AECOPD. One study showed that theophylline resolved $FEV_1$ faster than placebo[64] but 3 others showed that theophylline had no effect.[65–67]

In comparing $\beta$ agonists, albuterol given every 20 min seemed to provide an $FEV_1$ effect equal to albuterol given every hour,[68] and nebulized albuterol seemed comparable to subcutaneous terbutaline.[69]

In comparing $\beta$ agonists to anticholinergics, ipratropium had an $FEV_1$ effect similar to fenoterol.[70] In another study, ipratropium improved $P_{O_2}$ but not PFT values in a comparison with metaproterenol.[71]

In combination trials, albuterol plus ipratropium did not seem additive over albuterol or ipratropium alone.[72–74] Albuterol plus beclomethasone was also found to be no better than fenoterol alone.[75] Emphasizing a point made in the discussion above on chronic bronchodilator therapy, one study showed that if albuterol, theophylline, or ipratropium alone was pushed to an effective bronchodilator effect, addition of a second agent did not give further benefit.[76] In a large meta-analysis of administration techniques, no difference was found in bronchodilator effect if the drugs were given via metered-dose inhaler or via small-volume nebulizer.[77]

In summary, much of the evidence supporting the use of bronchodilators during AECOPD comes from studies of acute asthma. It remains unclear, however, whether higher doses of individual agents or combination therapies are more useful than standard dosing regimens of single agents.

Table 5. Steroids During Acute Exacerbations of COPD

| Study | *n* | Design | Results |
|---|---|---|---|
| Albert et al[78] | 44 | RCT | Steroids improved $FEV_1$ |
| Emmerman et al[79] | 100 | RCT | Steroids had no effect |
| Bullard et al[80] | 138 | RCT | Steroids improved $FEV_1$, not hospitalization rates |
| Thompson et al[81] | 27 | RCT | Steroids improved $FEV_1$ |
| Davies et al[82] | 56 | RCT | Steroids improved $FEV_1$, not subsequent walk test or $FEV_1$ |
| Niewoehner et al[83] | 271 | RCT | Steroids reduced treatment failures, not long-term outcome |

COPD = chronic obstructive pulmonary disease
RCT = randomized controlled trial.
$FEV_1$ = forced expiratory volume in the first second

### Corticosteroids

The rationale for corticosteroid therapy in AECOPD is that acute airway inflammation might respond to the anti-inflammatory effects of corticosteroids, as it does in asthma. Supporting that concept are a number of randomized clinical trials in AECOPD that showed that corticosteroids improved PFT values more rapidly and shortened the exacerbation period (Table 5).[78–83] Note, however, that

not all of those studies were positive. Moreover, although the short-term resolution of AECOPD may be enhanced with corticosteroids, the long-term outcome in one large trial did not seem different than placebo.[83]

### Antibiotics

The rationale for antibiotics is that infectious bronchitis is a major cause of AECOPD. Routinely giving antibiotics in AECOPD has been evaluated in a number of studies,[84–92] many of which showed that antibiotics shortened the severity and/or duration of acute exacerbation, but that finding was not universal.[87–91] In a meta-analysis in 1995, Saint et al[93] found a statistically significant effect in favor of routinely giving antibiotics.

### Noninvasive Positive Pressure Ventilation

Severe exacerbations of COPD can lead to respiratory failure and the need for mechanical ventilation. It is conceivable that if short-term muscle rest could be achieved with NPPV through a nasal or oral mask, the pharmacologic agents given for AECOPD might be given time to work and thus avert the need for invasive mechanical ventilation. Evaluating this concept are a number of randomized and/or crossover trials that used NPPV in the initial phases of severe AECOPD.[94–98] Although there are mixed results, both of the largest studies of NPPV in AECOPD[97,98] found that NPPV reduced the need for invasive mechanical ventilatory support.

### Summary

In summary, both chronic and acute COPD have a number of therapeutic options available to clinicians. For the long-term management of the disease, a number of agents have been shown in short-term studies to improve PFT values. Though the long-term clinical benefits of this would seem intuitive, remarkably few data exist showing that long-term outcome in COPD is significantly affected. Nevertheless, symptom improvement and dyspnea reduction are certainly strong reasons to use those agents. The 2 most compelling bodies of evidence in stable COPD are for oxygen therapy in the chronic hypoxemic patient and the use of pulmonary rehabilitation to improve exercise tolerance and dyspnea. Inhaled corticosteroids also appear to be useful in patients at risk for frequent exacerbations.

In AECOPD, the rationale for therapy comes in part from the large body of literature on acute asthma therapy. Bronchodilator therapy and corticosteroids both seem to reduce the severity and duration of exacerbations. Moreover, routine antibiotic use seems beneficial, and the role of NPPV in patients with impending respiratory failure from AECOPD seems well supported by the literature.

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## Discussion

**Rubenfeld:** Neil, that was yeoman's work. I have a question. In putting that together, one of the things that you necessarily have to gloss over is that you've lumped together a lot of different kinds of outcomes, and I think you had to in the 30 minutes you were allotted. But what do you think the important outcomes are in that study? A lot of those studies seem to use spirometric outcomes. Do you think that's a useful outcome in interpreting COPD evidence?

**MacIntyre:** I thought Gordon [Guyatt] hit the nail right on the head this morning. I think physiologic end points have to be viewed with a great deal of caution. $P_{O_2}$ as an end point unto itself is something we've got to get rid of. Obviously you have to have a certain $P_{O_2}$ to live, but once you've accomplished that, attempts to further improve $P_{O_2}$ usually end up creating more problems than they're worth. I'm not sure I can say the same thing about $FEV_1$, although perhaps I could. $FEV_1$ is a marker of a disease. COPD is a disease of airflow obstruction, and $FEV_1$ is a measure of the degree of obstruction. There are a number of studies that correlate functional capabilities, quality of life, and even mortality with $FEV_1$, so $FEV_1$ probably is not a bad surrogate for airway function. But having said that, it is a physiologic end point and thus fraught with potential danger; I think $FEV_1$ is probably a reasonable physiologic surrogate.

**Guyatt:** I think one of your slides—the one in which an investigator pulled together a few studies and made a big deal about very small changes in $FEV_1$—highlights its limitations. I would agree with what's implied in Dr Rubenfeld's question—that if you could improve somebody's $FEV_1$ by a liter, it would be an adequate surrogate end point. However, the trouble is that most of those studies looked at small differences; even when they find positive effects, they're looking at $FEV_1$ differences of 50 mL or sometimes 25 mL. The clinical importance of those differences is extremely questionable. I believe that convincing evidence must come from measures of quality of life, symptoms, exacerbations, hospitalizations, and other outcomes that I would characterize as "patient-important outcomes."

**MacIntyre:** I would certainly agree with that. In the lung-volume-reduction surgery trial, the end point was not $FEV_1$; it was mortality and exercise capability. $FEV_1$ was a secondary end point. And in reviews of pulmonary rehabilitation an almost universal finding is that $FEV_1$ rarely changes at all; even though patients have functional improvement and their quality of life goes up and dyspnea goes down, their $FEV_1$ doesn't change at all. So having said that, I thought $FEV_1$ was a legitimate surrogate for airflow properties. As for whether small changes in $FEV_1$ mean anything in real life, I think the point's well made that they may not. You need a substantial amount of $FEV_1$ improvement to translate into meaningful clinical outcomes.

# Letters

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## The Future of Respiratory Care

I just read David Pierson's masterful article on the future of respiratory care.[1] How shocking it is to think how fast 30 years have gone by. But as the saying goes, "time flies whether you're having fun or not." That's why I think we should have fun as we pursue our professional and personal lives.

Those were great days in the early 1970s when we were on the steep slope of the "work/accomplishment curve" (very much like the oxyhemoglobin dissociation curve). Lots of things began in that era, such as long-term oxygen therapy, pulmonary rehabilitation, and the acute respiratory distress syndrome (ARDS). The recognition of ARDS and the establishment of principles of its management revolutionized our approach to the treatment of acute respiratory failure and multiple-organ system failure. These were the foundations for modern-day critical care.

Quite frankly, I don't see the same rate of progress today. But, of course, the easy stuff is now "old hat."

I recently heard that the National Institutes of Health have spent billions of dollars—some say as much as $60 billion—on research on the mechanisms of acute lung injury resulting in ARDS. It is amazing that the only real advance in outcome was from the ARDS Network controlled clinical trial, which compared low and high levels of tidal volume during mechanical ventilation.[2] It is only through controlled clinical trials that we will continue to make major progress in ARDS.

The success of the Seattle group in ARDS management is interesting. The improved survival[3] reported before the *New England Journal of Medicine* article by the ARDS Network[2] must have been due to more disciplined care in the Harborview unit than is possible in most places.

I am greatly concerned when I visit and make intensive care unit rounds in many places in this country. It seems like everyone in the unit who is receiving mechanical ventilation is sedated and paralyzed. I once commented about this.[4] What is even worse is that the attendings don't even examine the patients. They stand outside the room and make pronouncements about care decisions without ever looking at or touching the patients. This is so different from the way it used to be. We always had our patients awake and alert so we could talk with them. We made rounds at 7:30 AM so that the daily game plan could be outlined. We made sure that the long-term ventilator patients were near the east windows so that they could see the sunrise. We always talked to them about the beginning of another day. Even if they were ventilator bound, we would walk them in the hall, or at least sit them in a chair. None of this could be done with sedation or paralysis. Quite frankly, I don't see the reason for paralysis and sedation in awake and otherwise cooperative patients. I believe it is a matter of convenience for the caregivers, which is not in the best interests of the patient. We encouraged the eating of food, rather than delivery of calories by nasogastric or percutaneous enterotomy tube or by the intravenous route.

For the future I see more advances in our ability to provide lifesaving care for critically ill patients. As we understand the mechanisms of sepsis, traumatic, and aspiration lung injury, and learn more about overwhelming infections, we will be able to deal with the basic underlying biologic processes that cause ARDS.

In another realm, I see the National Lung Health Education Program making great strides in its partnership with the American Association for Respiratory Care. I really think that we can implement an early diagnosis and treatment grassroots movement around the country for chronic obstructive pulmonary disease (COPD) and related disorders.[5] By getting spirometers in all offices of both primary care physicians and certain specialists (eg, cardiologists) who deal with patients with smoking-related disorders, we can make major inroads into the COPD problem, as well as related lung cancer. We just have to put our mind to it. We have the knowledge and technologies to change the outcome of both COPD and lung cancer through early identification and intervention.

I am very gratified by what Dr Pierson has done for the Journal. Now that it is indexed by *Index Medicus* and traceable through reference sources, many more people around the world will be kept abreast of the rapidly growing advances that are immediately before us.

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# Books, Films, Tapes, & Software

**Decisions and Evidence in Medical Practice: Applying Evidence-Based Medicine to Clinical Decision Making**. Richard Gross MD. St Louis: Mosby, 2001. Soft cover, 264 pages, $39.

As the title suggests, **Decisions and Evidence in Medical Practice** integrates evidence-based medicine with clinical decision-making. The book is divided into chapters according to whether the evidence is about treatments, diagnostic testing, risk, or prognosis; or in the form of overviews, guidelines, pathways, or decision analyses. Each chapter has sections on the components of decisions (interpreting statistics), evidence (retrieving information and evaluating its validity), and helping the patient decide (decision-making).

This organization contrasts with the traditional organization by study design. Thus, both case-control and cohort studies appear in the chapter on risk, whereas cohort studies also appear in chapters about treatments and prognosis. Techniques for decision-making are found under treatments and diagnostic testing as well as under decision analysis.

Examples from published literature or well-constructed hypothetical situations illustrate points. Short exercises throughout the text allow the reader to practice calculations and enhance understanding. Clinical scenarios in a final chapter give an opportunity to apply the entire process, from formulating a question to patient care. An appendix summarizes techniques so they can be employed rapidly.

This book provides an excellent discussion on finding evidence, with clear directions for searching MEDLINE efficiently and a thorough review of electronic sources of evidence. Other strong sections include the explicit instructions for helping patients assign utilities and the thoughtful approach to discussing prognosis with patients. The author displays bias toward systematic reviews over individual trials and cohort studies over case-control studies, but also a healthy skepticism about practice guidelines. There is more repetition than one would expect from a single-author text, with randomization, concealment, and run-in being presented twice.

The readership is said to be students, postgraduate trainees, or seasoned practitioners (sometimes referred to more specifically as "physicians"). Yet the author felt the need to define chronic atrial fibrillation ("a common type of rapid and chaotic heart rhythm"), pulmonary embolism ("a blood clot lodged in the larger arteries of the lung"), and deep vein thrombosis ("a large blood clot in the leg").

The aim is to provide an introduction to several topics, so many things are simplified. Readers are urged to search peer-reviewed compendia of evidence (such as *Best Evidence* or the Cochrane Library) before PubMed. Some terms are substituted for standard terms (*follow-through rule* for *intention-to-treat analysis*; *action threshold* for *risk-benefit ratio*). Such terms as *referral bias*, *surveillance bias*, and *vote count* are not used at all, although examples illustrate their concepts. The definition for *likelihood ratio* is more intuitive than usual. Avoiding jargon and excluding symbolic notation makes the book approachable, but readers may be confused when they move to other texts that use conventional terminology.

There are many mnemonics that were new to me. However, some seem confusing. *PID* is used to mean *positive in disease*, *AID* for *abnormal if diseased*, and *NIH* for *normal in health*. But how do we remember which describe sensitivity and which specificity? Other mnemonics seemed strained; for example, *SnNout* (*sensitive tests when Negative rule disease out*) and *SpPin* (*specific tests when Positive rule disease in*).

I tried to contrast criteria for the validity of evidence presented here with those presented elsewhere. However, it was difficult to compare checklists one-to-one. In general, this book contains all the major criteria typically listed in other sources, but with different wordings, groupings, and emphasis.

Of course, the book is not as thorough as texts devoted to a single one of its components. With respect to statistics, it describes 95% confidence intervals for differences but not for ratios. Nowhere does it mention sample size, the power of a study to detect a difference, or type II error. As to evidence validity, this book omits objective assessment of outcomes from criteria for treatment and omits tests for homogeneity, objective data abstraction, sensitivity analysis, and subgroup analysis from criteria for meta-analyses. It says case-control studies are used when long-term exposure to a risk is needed before its effects become apparent, without mentioning long-term latency of the disease. And it omits cost as a consideration in clinical decision-making.

The book has wide margins and plenty of white space to ease reading and help organization. Its cover has a conservative design in attractive colors. Being paperback keeps its cost down. I found few typographical errors (eg, risks of 6.2% and 4% in one example somehow were transformed to 7.5% and 0.3% in the corresponding equation).

All the illustrations are line art. The 2 × 2 matrix for results of diagnostic tests arranges the accepted standard in rows, and test results in columns—opposite of the usual format. The meta-analysis plot gives no units on the horizontal scale, so the opportunity is lost to point out the increments for ratios versus differences. Some web addresses for systematic reviews and guidelines are presented in the text, but are not in the table listing sources of electronic evidence. References are at the end of each chapter rather than each section, so I had to flip through several pages to find them. The index helpfully cross-references acronyms to their expanded forms. Unfortunately, it may list only the nonstandard substitute term (*follow-through rule*) even when the standard term (*intention-to-treat*) is referred to in the text.

Anyone in clinical care seeking an introductory text on how to retrieve, evaluate, and apply medical evidence will find this book readable, interesting, and useful. However, those anticipating going deeper in these areas might do better to choose approachable books specifically about informatics, statistics, study validity, or clinical decision-making.

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**Evidence-Based Medicine: How to Practice and Teach EBM**, 2nd edition. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Edinburgh, United Kingdom: Churchill Livingstone, 2000. Soft cover (with CD-ROM), illustrated, 261 pages, $34.95.

This is the 2nd edition of one of the most popular introductory books on evidence-based medicine (EBM). The authors bring a wealth of experience in both practicing and teaching epidemiology and internal medicine, and they have published many other books and articles that explore areas of EBM in greater depth. As stated in the preface, this book is directed at the busy practitioner, being well described as "short, lean, and practical." It is geared toward clinicians, but paramedical professionals and students of epidemiology will find this book a useful resource.

The book has been rewritten since the first edition, into a case-based format. The initial chapters deal with asking answerable clinical questions and how to find the best evidence to answer those questions. Subsequent chapters deal with how to appraise information gathered, looking at several types of evidence: diagnosis and screening, prognosis, therapy, harm, and guidelines. Each chapter is organized in a format similar to the popular "Users' Guides to the Medical Literature" series published in *The Journal of the American Medical Association* (the series was recently updated and published in a book[1]), first considering the validity of evidence, then the impact or size of the effect, and then its applicability to clinical practice. Specific examples are given for each topic, using common, practical clinical problems. The final 2 chapters cover methods and suggestions for teaching EBM and evaluating the reader's success at practicing and teaching EBM.

Several other resources are provided with the book. There are numerous references throughout the book encouraging the reader to visit one of the authors' Web sites, http://www.library.utoronto.ca/medicine/ebm, which not only includes the information from the book but links to other references, updates, and programs to download for hand-held computers, to assist with some of the statistical calculations. (Several areas of that web site are still under construction, and input from readers is encouraged, so this resource will continue to expand and improve.) Also included with the book are several pocket cards that contain key points from each chapter and important tables, including a table to help calculate number needed to treat or harm and a nomogram for likelihood ratios. As well, there is a CD-ROM included that not only contains all the information from the textbook (the tables were a little difficult to read on my computer), but also contains other relevant examples in several other areas of medicine, which would be very helpful to those wishing to use the principles from the textbook in teaching EBM in areas of medicine other than internal medicine (these examples are also available on the Web site).

The book is written in an informative but informal style, with several personal anecdotes, and is very readable. Use of the case-based format makes the application of the principles clear; opportunities are provided and encouraged for the reader to attempt to answer the questions presented in the book prior to reading the authors' answers. I highly recommend having a computer with access to the Internet and on-line databases while reading this book, particularly when reading Chapter 2, which is on how to find current best evidence. The chapter provides a lot of valuable tips for improving search techniques and suggests several methods of improving the yield of relevant, current evidence. The reader is encouraged to practice the search strategies while reading the chapter. As well, suggestions to help the busy clinician keep up-to-date are provided near the end of the chapter.

All of the chapters are well written and concise, with many tables provided to highlight the main points. Chapters 3 through 6 are similar to the articles published in the aforementioned "Users' Guides" series, although they have been updated with new examples, and multiple examples are given in each subject. The therapy chapter also provides information on systematic reviews, clinical decision rules, and economic analyses. Multiple examples are provided for some of the more difficult topics, especially number needed to treat and how to apply that to a specific patient (whose risk of the outcome under consideration may differ from the "standard" patient) using a decimal fraction.

One subject that might have been dealt with in greater depth was the difference between odds ratios and relative risk ratios and how to convert between the two and number needed to treat. The two are both introduced, but instead of defining the differences between them (which I find is a common question from students and residents), formulas are provided to convert either term into a number needed to treat. A table is provided with formulas (Table 5.11), but the format is confusing. However, readers wishing a more in-depth coverage of those issues can look to other books by two of the same authors,[2] and I suspect this topic was covered in less depth in the interest of readability and space. References are provided with each chapter for those who wish to pursue certain topics in greater depth.

I particularly enjoyed the chapter on guidelines (Chapter 7), which provided a very practical approach to assessing guidelines, and the strong emphasis on applying guidelines to a specific population. The 4 potential "killer-Bs" (Burden of illness, Beliefs of individual patients, Bargain [looking at the cost], and Barriers) provide a practical and memorable way of looking at the applicability of a guideline to the reader's setting.

The chapter on teaching methods is quite extensive, considering the brevity of the book, with tips for teachers of EBM in many settings, and a "monster" table of tips for teaching EBM. This adds to the teaching methods presented in other chapters, which are marked out with mortarboard symbols throughout the book.

Two appendixes are included with the book: one dealing with confidence intervals, including sample calculations, and the second is a glossary of common EBM terms. There is an index, which appeared to include all the important topics, although the organization of the book is so clear that I found I did not use the index much, as information was easy to find.

Overall, this book is very well written and clearly organized. Tables are well laid out and clear, and symbols are used to indicate when the reader should refer to the pocket cards and to indicate where specific teaching tips are located in each chapter. Readers are also encouraged to visit the Web site to provide feedback on any areas requiring clarification. For those wanting a readable and concise introduction to EBM, this book is an excellent choice. Because of its pocket-sized format, those who wish to study certain areas in greater detail may need to look elsewhere (although perhaps only as far as the references provided by the authors).

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**Introduction to Research in the Health Sciences**, 4th edition. Stephen Polgar MSc and Shane A Thomas Dip Pub Pol PhD. London, United Kingdom: Churchill Livingstone, 2000. Soft cover, illustrated, 322 pages, $41.

Learning to do research is like learning to ride a bike: reading a book is not much help. You have to learn by doing under the guidance of an experienced mentor. Yet the student of health sciences research must be familiar with basic concepts that can be studied by reading. The trick is to select the right topics and present them in a way that is both relevant and interesting. The authors of this book are faculty members of the School of Public Health, La Trobe University, and the School of Nursing, Deakin University, in Melbourne, Australia. They have done a remarkable job performing this trick. I began my review by trying to skim and summarize each chapter. But I kept getting engrossed in the examples and discussion questions. Before I knew it, I had read the book cover to cover.

The layout of the book makes it unusually easy to read. There are 21 "bite-sized" chapters (averaging about 10 pages) divided into 7 sections. This makes it easy to get a good initial understanding or to quickly review a topic. The authors make liberal use of figures, tables, and lists. Section 1 reviews the philosophical foundations of the scientific method. Section 2 covers research planning. It describes sampling methods and the concepts of internal and external validity. Section 3 describes the strengths and weaknesses of various experimental and quasi-experimental research designs. There are chapters on surveys and qualitative field research. Of particular interest is a chapter explaining "*n* of 1" study designs, which are becoming popular in the evidence-based medicine literature.

Section 4 covers the various aspects of data collection, with particular emphasis on questionnaire design and interview techniques. There is a chapter on measurement and instrumentation, which has good explanations of reliability and validity. However, I felt this chapter was a little weak and slanted toward the instruments used in behavioral research. It should have described the basic devices used to make physical measurements in health care, instrument error, calibration, and agreement/accuracy studies. This is particularly important, as most allied health research, especially in the field of respiratory care, involves device evaluation studies. Another pet peeve of mine that was not addressed is the actual recording of data during experiments. Novices often waste much work because they do not appreciate the mechanics of keeping a laboratory notebook or comparable computer files.

Sections 5 and 6 are fairly standard reviews of descriptive and inferential statistics. The chapter on interpretation of the evidence is particularly well done and explains the difference between statistical and clinical decision-making. One minor criticism of these sections is that the numerous figures illustrating frequency distributions are rather crude in that they are shown as polygons rather than smooth, asymptotic curves drawn from the underlying mathematical model. Of more concern, I believe, is that the techniques of analyzing data from device evaluations (eg, accuracy and agreement studies) are not mentioned. This is a specialized set of statistical techniques that are not difficult to understand but are frequently misapplied. As mentioned before, device evaluation studies play a major role in allied health research.

Section 7 covers the publication of research results. One chapter describes the basic format of research publications (introduction, methods, results, discussion) along with some useful tips for writing and getting your work published. The other chapter in this section perhaps summarizes the key purpose of this book: the critical evaluation of published research. Few people who read this book are destined to become published research scientists, but hopefully they will all be more educated consumers of research literature. As the authors say in the introduction "... health professionals participate in a 'culture' that privileges knowledge based on the critical review of scientific evidence. In order to participate in discourses concerning health problems and their treatments, practitioners need to understand the ... 'rules' of evidence ..." This chapter shows how many of the concepts of performing research come into play in just reading an article. There are sub-sections that show how to critically review the introduction, methods, results, and discussion of a paper, with an outstanding table showing potential problems and their implications. There is even a brief introduction to meta-analysis.

Section 8 contains a very useful glossary, which I have found to be unique for this type of book. The index is detailed and appropriate. Indeed, it is the supporting material that makes this textbook really useful. (The authors even give an e-mail address and offer Internet-based teaching materials.) At the end of each chapter is a set of self-assessment questions (true/false and multiple choice, with answers in the back of the book). Even better, at the end of each section are several pages of discussion. These discussions set up hypothetical research situations and ask the reader questions that involve the use of the concepts presented in the section. Each question has a detailed answer that gives the reader a sense of having a mentor looking over his shoulder giving help and encouragement. In fact, the text throughout is worded in almost a conversational style, with many simplified examples from real world experiments. This helps to illustrate the relevance of each new concept, which might otherwise seem dull and abstract.

I own 5 textbooks on introductory research in allied health, including one I wrote myself. This is the one I will refer to most often. I would recommend this book, not only for classroom use, but also for self-study by anyone practicing a health care profession.

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**Evidence-Based Asthma Management**. J Mark Fitzgerald MD, Pierre Ernst MD MSc, Louis-Philippe Boulet MD, and Paul M O'Byrne MB, with 31 other contributors. Hamilton, Ontario, Canada: BC Decker, 2001. Hard cover (with CD-ROM), illustrated, 326 pages, $89.95.

It is an interesting comment on how far we have come that a textbook on asthma differentiates itself from others in the field by calling itself "evidence-based." Eighteen years ago, my medical school's dean said, "Half of what we are going to teach you is false; we just don't know which half." The

rapid change in our understanding of asthma illustrates that truth. A systematic examination of the evidence on which our practice is based can help us to understand how solid—or shaky—is the ground on which our current truth stands.

To illustrate some of the rapid changes over the last decade: We used to think of asthma as a disease of "hyperreactivity" of bronchial smooth muscle. Now we believe inflammation is the underlying process.[1] We had believed that severe viral infections can predispose to asthma.[2] Now the "hygiene hypothesis" suggests that lack of infections in infancy can predispose to the development of asthma.[3]

A critical review of how we know what we know is important. Levels of evidence are categorized as Level I (evidence from randomized clinical trials), Level II (evidence from well-designed cohort or case-control studies), or Level III (expert opinion). Therapeutic recommendations are graded as A through E. A is defined as good evidence to support a recommendation for use. C is poor evidence to support a recommendation for or against use. And E is good evidence to support a recommendation against use.

This book struggles with 2 stories running concurrently: the story about what is known about asthma and the story of how good is the evidence. The authors use various styles to present these co-existing stories and differ in how much emphasis they place on each. Should the chapters be a review of the state of the art? Should they highlight the best evidence? Or should they highlight where evidence is lacking?

Several authors approach the challenge with "evidence-based review articles," the salient points of which are highlighted by reference to evidence level. One author took an innovative approach by starting with a brief introduction and then discussing the pertinent Level I evidence, Level II evidence, and Level III evidence under separate subheadings. This presentation style makes it easier for the reader to discern the quality of the evidence within each subject discussed.

Another author presented a table summarizing key recommendations of various management components, followed by an "evidence-based recommendation." For example, the evidence-based recommendation given under "inhaled glucocorticoids" is "the most effective medications for prevention of asthma symptoms (Level IA)."

Another author approached the task by summarizing the evidence and then making a therapy recommendation, appending the evidence level to the recommendation. For example, the section subheaded "Noncompliance" discusses the evidence supporting noncompliance as a reason for asthma unresponsive to usual therapy. Then under the subhead "Recommendation," the author states, "Patients thought to have unresponsive asthma should have their compliance with antiasthma therapy verified by whatever means is feasible (eg, a review of pharmacy records) (Level IIA)."

One of the dangers of a book such as this is that major new evidence will surface by the time of or shortly after publication. One of the more glaring examples of this is the claim that "There are no prospective, randomized, rigorously controlled, double-blind studies of the effect of inhaled glucocorticoids on long-term linear growth." That deficiency has been addressed by the recently-published results of the Childhood Asthma Management Program study, a prospective randomized study that followed asthmatic children treated with budesonide, nedocromil, or placebo, for 4–6 years.[4]

Other chapters avoid this difficulty by referencing studies in progress. For example, the chapter on the role of inhaled corticosteroids states: "These studies suggest that inhaled corticosteroids can diminish the decline in airway function . . . Each of these studies, however, has limitations . . . This has led to the development of a large, multinational, prospective, randomized, and placebo-controlled study of the effects of early intervention with inhaled corticosteroids . . . This study, known as the START (Steroid Therapy As Regular Treatment) trial, will evaluate the potential beneficial effects of inhaled corticosteroids treatment started within the first 2 years of the development of asthma . . ."

Information presented is generally consistent with what is currently regarded as state of the art. However, grading of the quality of the "state of the art" is not consistent. References are not always provided to the papers with the supporting evidence. For example, one author states that "Treatment of exacerbations is most often accomplished by geometrically increasing the dose of inhaled corticosteroids by a factor of two- to four-fold and, if the exacerbation is more severe or non-responsive to the increased inhaled corticosteroid, adding ingested corticosteroids (Level I)." The author is exactly on target that excellent evidence supports the effectiveness of systemic corticosteroids in treating more severe asthma exacerbations. However, the implication that Level I evidence supports the use of 2×–4× increased doses of inhaled corticosteroids is not accurate.

A CD-ROM is included with the book and reproduces the content of the book. This may aid in searching for particular pieces of information or in sharing information with colleagues. This use, however, does not start to tap the potential of a CD-ROM. If abstracts of the literature referenced (perhaps with links to PubMed embedded) had been included in the CD-ROM, it would have helped the CD-ROM realize more of its potential value.

**Evidence-Based Asthma Management** is written by a distinguished series of authors, and its 25 chapters cover the breadth of asthma management issues. Chapters cover natural history, epidemiology, genetics, and pathology. There are excellent discussions of the difficulties in making the diagnosis in adults and children. Asthma triggers in the indoor, outdoor, and occupational environment are covered. The provocative data on the role of childhood infection is discussed. Chapters discussing principles of asthma management in adults and children are followed by discussion of the roles of each class of medication. Controversies in the management of severe, life-threatening, and unresponsive asthma are well covered. Asthma education and outcome measures are discussed only briefly, but the framework presented is valuable.

Complementary and alternative therapies are not discussed in the book. This is an unfortunate omission, because patients often seek out those therapies.[5]

This book is not an introductory text for individuals with limited background in asthma. It is a survey of the evidence supporting our current practice. It is valuable reading for any health care professional who wants to explore the evidence underlying current asthma practice recommendations. It is also an important reference for asthma management, for preparation of local asthma care guidelines, for preparation of talks, and for locating important publications. Examination of the various styles used by the authors may

also help future authors of evidence-based reviews decide on presentation style.

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**Medicine Meets Virtual Reality 2000. Envisioning Healing: Interactive Technology and the Patient-Practitioner Dialogue**. James D Westood, Helene M Hoffman, Greg T Mogel, Richard A Robb, and Don Stredney, Editors. Amsterdam: IOS Press. 2000. Hard cover, illustrated, 402 pages, $101.

This book is a compilation of papers submitted at the eighth annual *Medicine Meets Virtual Reality* conference held in January 2000—a publishing opportunity for conference presenters, mostly physicians. At the time of the writing of this review, the next annual *Medicine Meets Virtual Reality* meeting had already taken place (January 2001).

Of more than 70 "chapters" none have direct relevance to respiratory care or pulmonary medicine. It is difficult to discern a theme or pattern in the editors' selection and ordering of chapters, and the topics range from medical imaging to acupuncture to tooth cleaning. The papers are not divided into topical sections, as would be expected in a typical text with many contributing authors.

This is not a book for mainstream respiratory therapists or most physicians. This is a compilation of short papers (restricted to 7 pages) on the general theme of virtual reality in medicine.

Chapter topics with the strongest relevance to respiratory care include:

•Immersive virtual reality: a description of a collaborative initiative to create a flexible, highly realistic simulation environment to train military surgeons, emergency/physicians, and physicians in rural areas. Multiple technologies are employed at once, including intentional psychological stressors.

•WebSTer: a World Wide Web-based virtual reality surgical training system that provides real-time manipulation of simulated surgical tools. The convenience and wide availability of the Internet were judged to be more important than authentic simulation of reality, making this project unique among the contributions. This project is one of the few in the book making mention of a thorough instructional goal analysis, an essential and too often overlooked plank in the development of technology-based instruction. That is, emerging multimedia technologies are so seductive that they often lead developers to entirely forget the original purpose of a project, to teach a defined knowledge or competency.

The book has a handsome cover but is otherwise not aesthetically pleasing. Fonts, font sizes, spacing, and other formatting elements vary from chapter to chapter. Particularly troublesome is that much of the book is printed in a terribly small font size, a substantial drawback for the reader with poor close vision. The graphics are entirely black and white. Though some images are impressive and most are acceptable, some are of remarkably poor quality. A few cannot be deciphered at all. There is no subject index, although there is an index of authors.

The writing styles differ markedly among the chapters, although most are written in a scientific-technical style with an abstract, and introduction, methodology, results, and conclusions sections. In some chapters, the language is quite stilted. For example: "In this context, there emerges the need to favour the possibilities of intervention on psychological dysfunctions by overcoming the limits that render the cost-benefit ratio disadvantageous . . " (p 357)

Even the tedious chapters are mercifully short, and it is possible to skim the material quickly and find topics that are intriguing, although not rigorously addressed. The field of respiratory care once enjoyed an early advantage in developing and applying computer-based-training and computer-managed branching-logic simulations. However, these aging technologies are crude indeed, given the hints of the marvelous things that may come when some of the futuristic ideas described in this book are realized.

As an instructional technologist and a respiratory therapist, I found this book to be mildly interesting. At more than $100, it might be of passing interest to educators following cutting edge medical instructional technology development, but would not be a top choice even for this narrow subject area.

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**Super Searchers on Health & Medicine: The Online Secrets of Top Health & Medical Researchers**. Susan M Detwiler. Reva Basch, Editor. Medford, New Jersey: CyberAge Books. 2000. Soft cover, 190 pages, $24.95.

This book is one of a series of interviews with experts in various fields. An author chooses prominent figures in the given subject area and then tries to find out what their secrets are for using the many electronic and on-line resources available in each field today. It attempts to give casual or new users a glimpse at expert techniques. Other volumes in the series address news, finance, legal, and business topics.

The health and medicine experts interviewed included medical librarians, physicians, an individual with a masters degree in business administration, and a photographer. Several own businesses that provide medical information for a fee to researchers, attorneys, and the public. The viewpoint changes considerably throughout the conversations. In fact, these seem not so much interviews as transcriptions of old friends having chummy conversations over coffee. At several points the reader might feel left out of an inside reference.

The medical librarians serve vastly different audiences, from clinical research and

patient education to patents and trademarks in industry. In general they stress the importance of interviewing the requester and finding out what question they are trying to ask. MEDLINE, EMBASE, and BIOSIS were considered starting points for most searches, with the *Cumulative Index to Nursing and Allied Health Literature* and ERIC being added for allied health and education/adolescents, respectively. Each had developed a type of checklist to remind them of good resources as well as pitfalls.

Evidence-based medicine was discussed by several people. It was entertaining to read one physician stating how this may help improve patient care but that he doesn't try to teach it to the medical faculty, since these are "tools to be taught to future practitioners." It sounds like the "old dog" adage at work.

Another physician provides an on-line resource for members of a national health organization. His job is to respond to e-mail queries from patients and moderate some of the on-line discussion groups. He brings to light several ethical issues regarding patient-physician communication via e-mail and the Internet. He commonly warns his users that information from a commercial Web site or one that asks for a fee should be treated as suspect. He also advises checking the Web sites for medical literature references. Typically more references indicate better authority.

Almost all of the participants expressed a feeling of loss when ELHILL, the command line search engine for MEDLINE, was shut down in 1999. The current Web-based interface doesn't allow simple use of qualifiers, adjacency, or step-by-step search strategy construction. Several also stressed the need for an improved taxonomy or language in order to better use a hierarchical approach to searching.

The appendix includes a list of Internet resources. Since the list was compiled over a year prior to this review, the quality of the choices was apparent. Surprisingly, all of the sites listed in the consumer section were still reachable, even though several had moved or been purchased by other companies. A random check in other sections gave the same result. The only failed link was found at national.chiropractic.edu. As an added convenience, all of the links are listed on an associated Web site, which should provide current information.

Overall, the book has too intimate a tone, resulting in excess verbiage. The main points that each participant makes are quite valuable, and their summary is all that is really needed. In fact, rather than spanning nearly 200 pages, a pamphlet with these 60-odd items summarized would be sufficient.

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# RC Web Sites

Steven B Nelson MS RRT, Section Editor

## Evidence-Based Medicine: On-Line Resources

(reviewed July 1– August 10, 2001)

This and the next issue of RESPIRATORY CARE address evidence-based medicine (EBM), a still-developing method for patient care that takes advantage of the immediacy of information exchange provided by multiple on-line resources. EBM has been greatly enhanced by the popularity of the Internet as well as the on-line availability of many respected, print-based journals.

EBM allows practitioners to more precisely treat patients on an individualized basis. Its greatest shortcoming is that it depends heavily on the ability of the reader to critically evaluate the validity or authority of medical literature.

It seems only natural to look on-line to develop a better understanding of what EBM is. One of the on-line progenitors, based on the many links to it, is the World Wide Web site of the United Kingdom's National Health Services Research and Development Centre for Evidence-Based Medicine.[1] That site includes a short explanation of EBM, how and when to use it, and its limitations,[2] based on a 1966 editorial in the *British Medical Journal*.[3] That article points out that EBM is the use of evidence for patient treatment and outcomes, rather than a treatment flow chart.

A more complete on-line EBM course is available from the Michigan State University Department of Family Practice.[4] Its 5 chapters cover basic concepts and teach how to read diagnosis, therapy, prognosis, and meta-analysis articles for validity and pitfalls. The course includes a chart that explains the following formula:

*Usefulness of medical information*

$$= (relevance \times validity)/work$$

Relevance refers to the frequency of exposure to a clinical question. How often does a therapist encounter a given disease or condition? Validity refers to the source of the information. A colleague's opinion may have less validity than a review article but more than a sales representative's presentation. Assessing validity is a learned skill. Lastly, human tendencies appear to favor minimizing work. If a great deal of work is required to obtain information, it is less likely to be sought.

Many sites provide summary reviews or practice guidelines. The Agency for Healthcare Research and Quality[5] provides reports through its 12 affiliated institutions on the most common clinical topics, including asthma, ventilator weaning, and chronic obstructive pulmonary disease. The American College of Physicians-American Society for Internal Medicine[6] publishes bi-monthly reviews covering many areas of practice. They include a simple search engine that covers the journals since 1991. The *British Medical Journal* publishes an electronic version of the journal *Evidence-Based Medicine*,[7] which allows searching and browsing of full-text articles. All of those services are free. A fee-based service is provided through InfoRetriever[8] that provides the ability to download updates to a Windows-based computer or a Pocket-PC-type computer. The service does not work with Netscape versions prior to 6.0.

The leading source for summarizing current treatment protocols is the Cochrane Collaboration.[9] It "prepare[s], maintain[s] and promote[s] the accessibility of systematic reviews of the effects of health care interventions." The Cochrane reviews are synopses of current published information that has been culled to provide results only from studies that are determined to have used good research methods. Abstracts are available at no cost, but obtaining complete reviews requires a subscription. Cochrane centers are found in more than 15 locations around the world. Information is reviewed by thousands of volunteers in all areas of medical practice and published in multiple languages.

One of the largest problems is finding relevant works. For example, a recent Cochrane review searched the literature for intravenous aminophylline use in acute asthma attacks.[10] Of the 210 abstracts identified, 27 were found eligible for inclusion, and only 15 were included in the analysis. According to the abstract, the quality of those abstracts was found to be only moderate.

Similar difficulties were found by William Sibbald (one of the participants in the Journal conference proceedings published in this and the next issue of RESPIRATORY CARE) and his colleagues.[11] Their review of weaning techniques found 667 potentially relevant abstracts. Of the 228 that had weaning as the main subject, 48 addressed the mode of ventilation, 16 had relevant outcomes, and only 10 were controlled trials.

Additional difficulty arises with terminology. Maureen Meade (another participant) and her colleagues, in reviewing potential harm from critical care interventions,[12] had to search using such disparate terms as *microscopic lung injury*, *barotrauma*, *acute respiratory distress syndrome (ARDS)*, *subcutaneous emphysema*, *pneumothorax*, and *pneumomediastinum* to find the many problems associated with mechanical ventilation.

A similar example can be found using the PubMed Clinical Queries search engine.[13] Searches can be made for categories of therapy, diagnosis, etiology, and prognosis, with an emphasis on either sensitivity or specificity. Search word order and grouping can produce markedly different results. Table 1 shows the different results produced by using the 3 words *cadmium*, *exposure*, and *lung* under the etiology category.

A search with the terms *lung* and *dioxin* found 26 hits, whereas the terms *lung*, *inhaled*, and *dioxin* found 0 hits, and the terms *lung*, *respirable*, and *dioxin* found 1 hit. Clearly the search algorithms are not perfected to the point that natural language queries will generate reproducible results.

Attempts at producing departmental summaries abound on the Internet. The Department of Pediatrics at the University of Washington is one example.[14] Two critically appraised topics started the collection in 1997. Three were added in 1998 and again in 1999. One was added in February 2000. None have been added since. The enthusiasm of the staff to continually review literature and update the reports can wane without sufficient ongoing support.

With all the negative points listed here, how can one conduct a review while minimizing pitfalls? Meade and Richardson[15] advocate starting with a well-built clinical question that includes (1) patients of interest, (2) intervention under investigation, (3)

Table 1. Search Results

| Word Search Order | Emphasis | Citations (*n*) |
|---|---|---|
| cadmium exposure lung | Sensitive | 10 |
| cadmium exposure lung | Specific | 4 |
| exposure lung cadmium, exposure cadmium lung, cadmium lung exposure, lung exposure cadmium | Sensitive | 36 |
| exposure lung cadmium, exposure cadmium lung, cadmium lung exposure, lung exposure cadmium | Specific | 6 |

comparison intervention, and (4) clinical outcome of interest.

Ellrodt et al point out the need for more well-designed clinical trials,[16] and Rowe et al show how to detect biases and determine whether existing literature is "good enough" to use.[17]

Finally, several additional locations offer links to other resources, including critically appraised topics, POEMs (patient-oriented evidence that matters), clinical practice guidelines, reviews, methodologies, and tutorials.[18–21]

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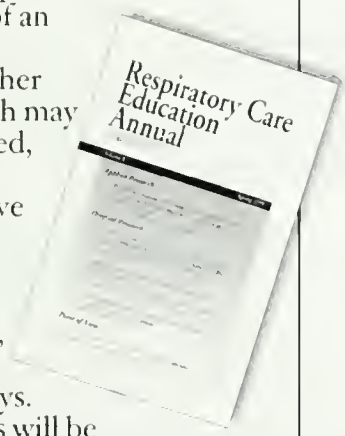
# Respiratory Care Education Annual Call for Papers

The Education Section of the AARC will publish Volume 11 of the *Respiratory Care Education Annual* in the spring of 2002. The annual is a refereed journal committed to providing a forum for research and theory in respiratory care education and is listed in the "Cumulative Index to Nursing and Allied Health Literature."

The AARC Education Section invites educators to submit papers for consideration. Preference will be given to papers that emphasize original research, applied research, or evaluation of an educational method. Other topics, which may be considered, include interpretative reviews of literature, educational case studies, and point-of-view essays. Submissions will be reviewed based on originality, significance and contribution, soundness of scholarship (design, instrumentation, data analysis), generalizability to the education community, and overall quality of the paper.




Deadline for submission is Dec. 1, 2001. Papers should be approximately 6–10 pages in length and should follow the guidelines in the "Publication Manual of the American Psychological Association, 4th Edition." Abstracts should not exceed 120 words. Mail submissions to AARC Education Annual, 11030 Ables Lane, Dallas, TX 75229-4593.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- Assisting with bronchoscopies and bedside tracheostomies
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Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

# Calendar of Events

| Date | AARC & State Society Programs | Contact |
|---|---|---|
| Nov. 3–4 | Asthma Disease Management Course, **Las Vegas, NV** | AARC, (972) 243-2272, www.aarc.org |
| Nov. 20 | Professor's Rounds 2001 Teleconference, Program 8 | AARC, (972) 243-2272 |
| Dec. 1–4 | 47th International Respiratory Congress; **San Antonio, TX** | AARC, (972) 243-2272, www.aarc.org |
| Feb. 6–8, 2002 | West Virginia Society for Respiratory Care's Winter Meeting; **Davis, WV** | Jay Wildt at (304) 442-7474 or jay.wildt@mghwv.org; or Anna Parkman at (304) 357-4837 or AParkman@ucwv.edu. |

| Date | Other Meetings | Contact |
|---|---|---|
| Nov. – Feb. | Deep South Center for Occupational Health and Safety offers an assortment of RC continuing education courses lasting from one to four days; **Birmingham, AL** | Melinda Sledge, University of Alabama at Birmingham, (205) 934-7178, www.uab.edu/dsc |
| Nov. 7–9 | Joint Commission Resources' 2001 National Conference; **Chicago, IL** | Customer Service Center, (630) 792-5800 |
| March 20–23, 2002 | 21st Annual Big Sky Pulmonary & Critical Care Medicine Conference; **Big Sky, MT** | American Lung Association of the Northern Rockies, (406) 442-6556, ala-nr@ala-nr.org |

## Coming in December

## Part II of the Special Issue on Evidence-Based Medicine in Respiratory Care

## 2001 Indexes

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Form Approved: OMB No. 0910-0291 Expires: 4-30-96
See OMB statement on reverse.

FDA Use Only (Resp Care)

Triage unit
sequence #



## A. Patient information

| 1 Patient identifier | 2 Age at time of event: or Date of birth: | 3 Sex | 4 Weight |
|---|---|---|---|
| In confidence | | ☐ female ☐ male | ____ lbs or ____ kgs |

## B. Adverse event or product problem

1 ☐ Adverse event and/or ☐ Product problem (e.g. defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other

| 3 Date of event (mo day yr) | 4 Date of this report (mo day yr) |
|---|---|
| | |

5 Describe event or problem

6 Relevant tests/laboratory data, including dates

7 Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

## C. Suspect medication(s)

1 Name (give labeled strength & mfr/labeler, if known)

#1

#2

| 2 Dose, frequency & route used | 3 Therapy dates (if unknown, give duration) |
|---|---|
| #1 | #1 |
| #2 | #2 |

| 4 Diagnosis for use (indication) | 5 Event abated after use stopped or dose reduced |
|---|---|
| #1 | #1 ☐ yes ☐ no ☐ doesn't apply |
| #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

| 6 Lot # (if known) | 7 Exp. date (if known) | 8 Event reappeared after reintroduction |
|---|---|---|
| #1 | #1 | #1 ☐ yes ☐ no ☐ doesn't apply |
| #2 | #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

9 NDC # (for product problems only)

10 Concomitant medical products and therapy dates (exclude treatment of event)

## D. Suspect medical device

1 Brand name

2 Type of device

| 3 Manufacturer name & address | 4 Operator of device |
|---|---|
| | ☐ health professional ☐ lay user/patient ☐ other |

6.
model #
catalog #
serial #
lot #
other #

5 Expiration date (mo day yr)

7 If implanted, give date (mo day yr)

8 If explanted, give date (mo day yr)

9 Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mo day yr)

10 Concomitant medical products and therapy dates (exclude treatment of event)

## E. Reporter (see confidentiality section on back)

| 1 Name & address | phone # |
|---|---|
| | |

| 2 Health professional? | 3 Occupation | 4 Also reported to |
|---|---|---|
| ☐ yes ☐ no | | ☐ manufacturer ☐ user facility ☐ distributor |

5 If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

# ADVICE ABOUT VOLUNTARY REPORTING

**Report experiences with:**

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

**Report SERIOUS adverse events. An event is serious when the patient outcome is:**

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

**Report even if:**

- you're not certain the product caused the event
- you don't have all the details

**Report product problems** – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

**How to report:**

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

**Important numbers:**

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

**If your report involves a serious adverse event with a device** and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

**Confidentiality:** The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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FDA Form 3500-back

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**5600 Fishers Lane**
**Rockville, MD 20852-9787**

# American Association for Respiratory Care **Membership Application**

### *ACTIVE MEMBER*
An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such; OR (2) is a graduate of an accredited educational program in respiratory care; OR (3) holds a credential issued by the NBRC.

### *ASSOCIATE OR SPECIAL MEMBER*
Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

### *STUDENT MEMBER*
Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

Please read the eligibility requirements for each of the classifications above, then complete the form. All information requested must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
  - ☐ Foreign
  - ☐ Physician
  - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name _____

First Name _____

Social Security No. _____

Home Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. ( _____ ) _____

**Work Information:**

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. ( _____ ) _____

Preferred Fax No. ( _____ ) _____

Preferred Email Address _____

Preferred mailing address: ☐ Home ☐ Business

Would you like to receive our monthly newsletter, AARC Report, by email?

☐ Yes ☐ No

Have you ever been or are you currently in the military?

☐ Yes ☐ No

## Demographic Questions (optional)

We request that you answer these questions in order to help us design services and programs to meet your needs.

**Primary Job Responsibility (check one only)**

- ☐ Director (Technical or Program)
- ☐ Supervisor
- ☐ Diagnostic Technologist
- ☐ Instructor/Educator
- ☐ Other, specify _____
- ☐ Therapist/Technician
- ☐ Medical Director
- ☐ Student
- ☐ Staff Nurse

**Type of Business**

- ☐ Educational Institution
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Hospital/Acute Care
- ☐ Other, specify _____
- ☐ Manufacturer or supplier
- ☐ Outpatient Clinic
- ☐ Physician office
- ☐ Skilled Nursing Facility

**Check the Highest Degree Earned**

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

**Number of Years in Respiratory Care**

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

**Job Status**

- ☐ Full Time
- ☐ Part Time

**Credentials**

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Date of Birth _____ Sex _____

***FOR STUDENT MEMBER – REQUIRED***

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. ( _____ ) _____

**Expected Date of Graduation (REQUIRED INFORMATION)**

Month _____ Year _____

**American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720**

# American Association for Respiratory Care Membership Application

## Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. These fees contain the $12.50 new members processing fee. Renewing members (except students) can deduct $12.50.

CHOOSE ONE LEVEL OF MEMBERSHIP

**1.** AARC REGULAR MEMBERSHIP (Receive both AARC Times and Respiratory Care journal)

| | |
|---|---|
| ☐ Active | $87.50 |
| ☐ Associate (Industrial or Physician) | $87.50 |
| ☐ Associate (Foreign) | $102.50 |
| ☐ Special | $87.50 |
| ☐ Student | $45.00 |

***OR***

**2.** AARC CHOICE MEMBERSHIP(Choose one publication)

| | |
|---|---|
| ☐ Active | $76.00 |
| ☐ Associate (Industrial or Physician) | $76.00 |
| ☐ Associate (Foreign) | $91.00 |
| ☐ Special | $76.00 |

I want ☐ AARC Times ☐ Respiratory Care journal

***OR***

**3.** AARC PLUS MEMBERSHIP (All publications and other items)

| | |
|---|---|
| ☐ Active | $122.50 |
| ☐ Associate (Industrial or Physician) | $122.50 |
| ☐ Associate (Foreign) | $162.50 |
| ☐ Special | $122.50 |

### *Specialty Sections (optional)*

Established to recognize the specialty areas of respiratory care, these sections publish a newsletter four times a year that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

| | |
|---|---|
| ☐ Adult Acute Care Section | $15.00 |
| ☐ Education Section | $20.00 |
| ☐ Perinatal-Pediatric Section | $15.00 |
| ☐ Diagnostics Section | $15.00 |
| ☐ Continuing Care-Rehabilitation Section | $15.00 |
| ☐ Management Section | $20.00 |
| ☐ Transport Section | $15.00 |
| ☐ Home Care Section | $15.00 |
| ☐ Subacute Care Section | $15.00 |

### PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

*NOTE. Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.*

**Signature** _____

**Date** _____

TOTAL MEMBERSHIP FEE $_____

TOTAL SECTION FEE $_____

**GRAND TOTAL = Membership Fee plus optional sections**

**$**_____

☐ Total Amount Enclosed $_____

☐ Please charge my dues (see below)

To charge your dues, complete the following:

☐ MasterCard

☐ Visa

Card Number

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Card Expires _____/_____

Signature _____

**Mail application and appropriate fees to:**

**American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720**

RESPIRATORY CARE

# Manuscript Preparation Guide

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to the following instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (available at *http://www.icmje.org/index.html*). Manuscripts are blinded and reviewed by professionals with experience in the subject of the paper. Authors are responsible for obtaining written permission from the original copyright holder to use previously published figures and tables. Before publication, authors receive page proofs and are allowed to make only minor corrections. Accepted manuscripts are copy-edited for clarity, concision, and consistency with RESPIRATORY CARE's format. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission. Editorial consultation is available at any stage of planning or writing: contact the Editorial Office, 600 Ninth Avenue, Suite 702, Seattle WA 98104, (206) 223-0558, fax (206) 223-0563, E-mail: rcjournal@aarc.org

### Categories of Articles

**Research Article:** A report of an original investigation (a study). Must include: Title Page, Abstract, Key Words, Introduction, Methods, Results, Discussion, Conclusions, and References. May also include: Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendixes.

**Review:** A comprehensive, critical review of the literature and state-of-the-art summary of a topic that has been the subject of at least 40 published research articles. Must include: Title Page, Outline, Abstract, Key Words, Introduction, Review of the Literature, Summary, and References. May also include: Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendixes.

**Overview:** A critical review of a pertinent topic that has fewer than 40 published research articles. Same structure as Review Article.

**Update:** A report of subsequent developments in a topic that has been critically reviewed in RESPIRATORY CARE or elsewhere. Same structure as a Review Article.

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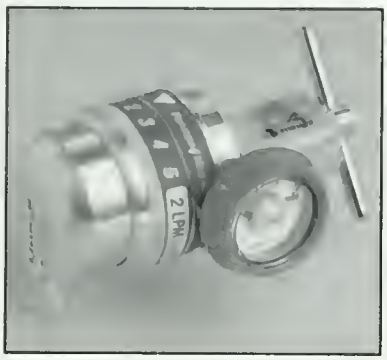

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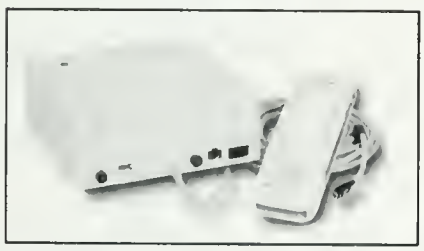

**Digital Amplifier.** SensorMedics has introduced the Cephalo digital amplifier, an all-purpose instrument used in both the sleep and EEG laboratories. It has recently received FDA approval, according to the manufacturer. The newly designed amplifier features built-in SaO2, 23 reference channels, 9 separate differential channels, and 8 DC channels, says SensorMedics. In addition, the SaO2 has been combined with the amplifier, reportedly reducing the space and cables needed in the lab. Data from and control information to the amplifier is transferred via a USB port. The maximum data collection rate is 1000 Hz, according to the manufacturer. For more information from SensorMedics, circle number 184 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

**Compact Stat Cart.** A compact stat cart from Nova Biomedical is specifically designed for use with the Nova Stat Profile® pHOx® blood gas and critical care analyzers in point-of-care applications. The manufacturer says that the compact footprint of the Stat Profile pHOx Cart allows the analyzer to be situated as near to the patient as possible and maximizes floor space at point-of-care locations, such as operating rooms and emergency departments. The pHOx Cart is equipped with a medical grade, uninterruptible power manager (UPM) that provides clean, conditioned power to the analyzer, reports Nova Biomedical, which also says that the UPM features built-in line conditioning and has up to 60 minutes of reserve time. Batteries are field replaceable and can be recharged in 24 hours. The manufacturer says that the UPM is compatible with all other Nova analyzers, in addition to the pHOx series. For more information from SensorMedics, circle number 185 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

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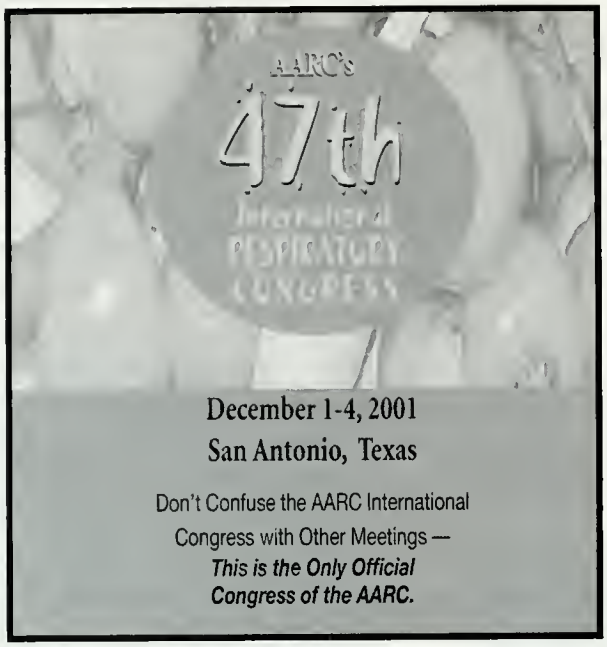


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1. Publication Title: Respiratory Care
2. Publication Number: 0020-1324
3. Filing Date: 10/1/01
4. Issue Frequency: Monthly
5. No. of Issues Published Annually: Twelve
6. Annual Subscription Price: $75.00
7. Complete Mailing Address of Known Office of Publication: Daedalus Enterprises, Inc. 11030 Ables Lane, Dallas, Dallas Co., TX 75229-4593
8. Complete Mailing Address of Headquarters or General Business Office of Publisher: Daedalus Enterprises, Inc., 11030 Ables Lane, Dallas, Dallas Co., TX 75229-4593
9. Full Names and Complete Mailing Address of Publisher, Editor, and Managing Editor:
**Publisher** — Sam Giordano, MBA, RRT, Daedalus Enterprises, Inc., 11030 Ables Lane, Dallas, TX 75229-4593
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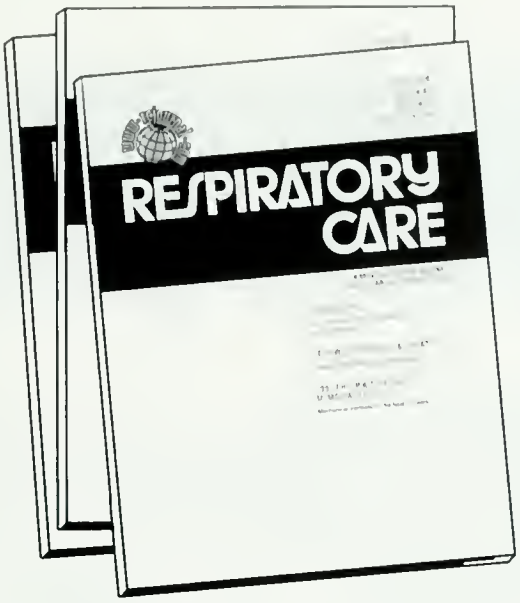


# *CRCE through the Journal—2001*

## Answer Key

For your information, the correct answers to the 50 question for *CRCE through the Journal*, which appeared in the September 2001 issue of RESPIRATORY CARE, are given below. Deadline for submission of answer sheets for CRCE credit was October 31, 2001.

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| 1. B | 11. D | 21. B | 31. D | 41. A |
| 2. A | 12. D | 22. C | 32. B | 42. A |
| 3. D | 13. B | 23. D | 33. D | 43. B |
| 4. C | 14. D | 24. C | 34. B | 44. C |
| 5. A | 15. B | 25. D | 35. C | 45. B |
| 6. A | 16. C | 26. A | 36. D | 46. D |
| 7. C | 17. A | 27. B | 37. C | 47. A |
| 8. A | 18. B | 28. D | 38. B | 48. C |
| 9. C | 19. D | 29. B | 39. A | 49. C |
| 10. C | 20. B | 30. A | 40. D | 50. C |

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Chuang, Kenneth H . . . . . 1258
Dauterive, Robin . . . . . 1258
Doyle, Daniel M . . . . . 1258
Edmonds, Marcia L . . . . . 1306
Ellrodt, A Gray . . . . . 1258
Farber, Harold J . . . . . 1307
Guyatt, Gordon H . . . . . 1201
Hess, Dean R . . . . . 1200, 1276
Hopper, Keith B . . . . . 1309
Landry, Michel D . . . . . 1226
Langham, Barbara . . . . . 1307
MacIntyre, Neil R . . . . . 1294
Maclean, J Ross . . . . . 1236
Mishoe, Shelley C . . . . . 1200, 1236
Montori, Victor M . . . . . 1201
Nelson, Steven B . . . . . 1309, 1311
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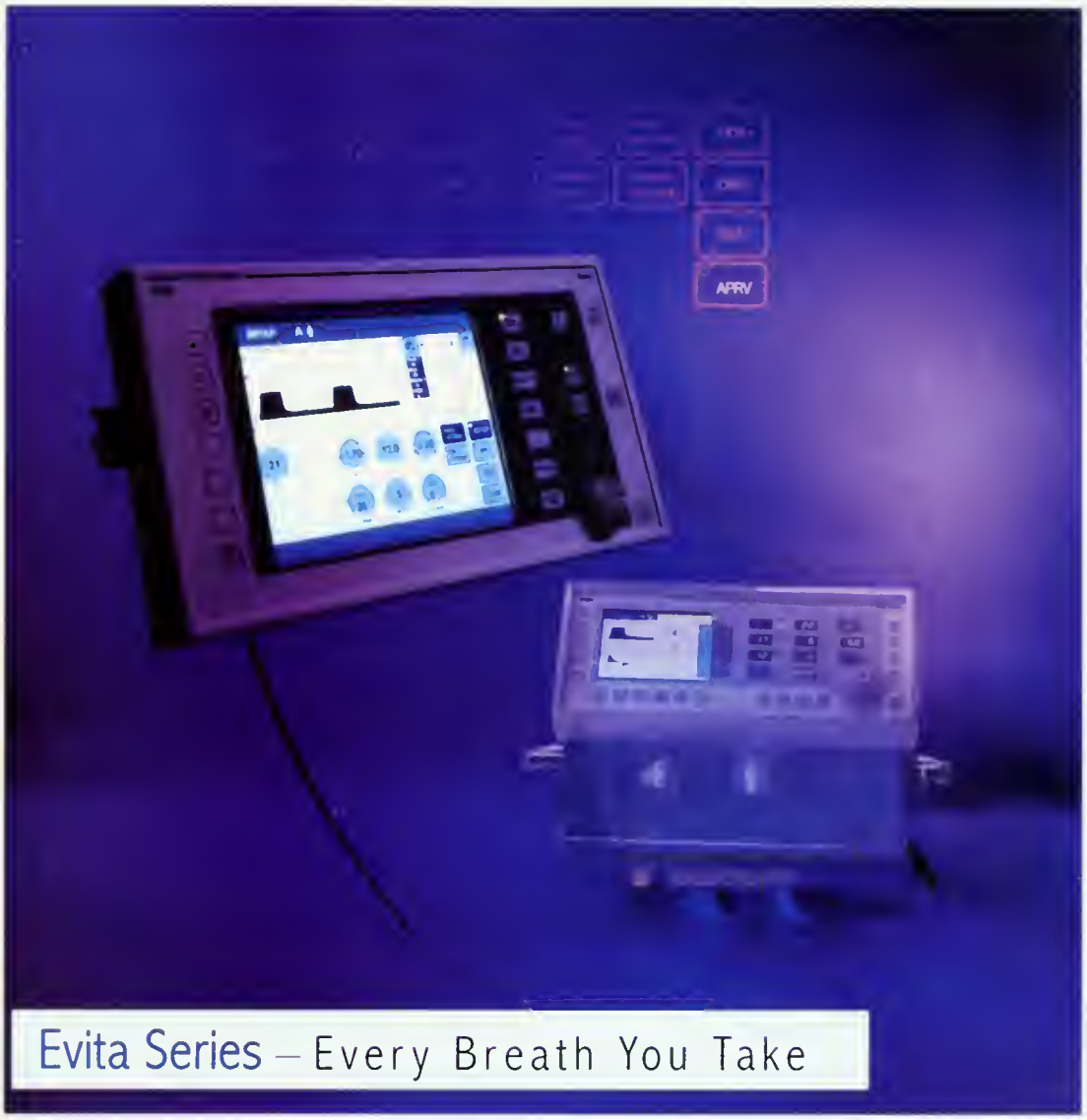


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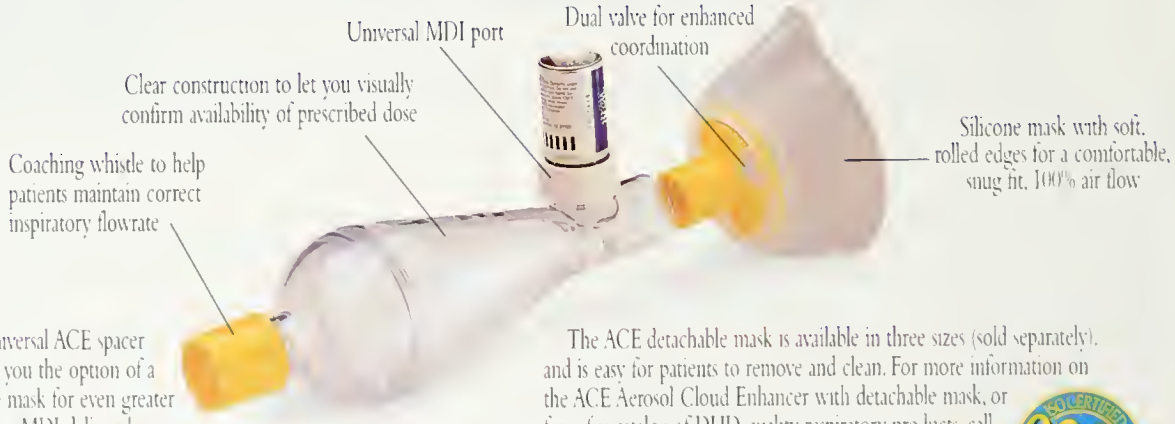
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